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Adenosine and Kidney Function

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Vallon, Volker, Bernd Mühlbauer, and Hartmut Osswald. Adenosine and Kidney Function. *Physiol Rev* 86: 901–940, 2006; doi:10.1152/physrev.00031.2005.—In this review we outline the unique effects of the autacoid adenosine in the kidney. Adenosine is present in the cytosol of renal cells and in the extracellular space of normoxic kidneys. Extracellular adenosine can derive from cellular adenosine release or extracellular breakdown of ATP, AMP, or cAMP. It is generated at enhanced rates when tubular NaCl reabsorption and thus transport work increase or when hypoxia is induced. Extracellular adenosine acts on adenosine receptor subtypes in the cell membranes to

affect vascular and tubular functions. Adenosine lowers glomerular filtration rate (GFR) by constricting afferent arterioles, especially in superficial nephrons, and acts as a mediator of the tubuloglomerular feedback, i.e., a mechanism that coordinates GFR and tubular transport. In contrast, it leads to vasodilation in deep cortex and medulla. Moreover, adenosine tonically inhibits the renal release of renin and stimulates NaCl transport in the cortical proximal tubule but inhibits it in medullary segments including the medullary thick ascending limb. These differential effects of adenosine are subsequently analyzed in a more integrative way in the context of intrarenal metabolic regulation of kidney function, and potential pathophysiological consequences are outlined.

I. INTRODUCTION

The kidneys play a central role in body homeostasis by adapting the renal excretion of fluid and electrolytes to bodily needs under the control of a systemic neurohumoral system. In addition to systemic control, primary intrarenal local regulation mechanisms are important for renal function and integrity. These local mechanisms are based on the way the mammalian kidney developed to fulfill its role in body fluid and NaCl homeostasis. More insights into intrarenal regulation of kidney function can provide a better understanding of pathophysiological processes and eventually new therapeutic approaches. Various autacoids are potential candidates to contribute to the signaling cascades involved in local regulation mechanisms including molecules like nitric oxide, bradykinin, endothelin, angiotensin II, and prostanoids to name a few. This review outlines the role of adenosine in the kidney. Before we focus on adenosine, we want to briefly introduce some aspects of kidney function to illustrate the need for intrarenal local regulation.

The way the mammalian kidney developed to fulfill its role in body fluid and NaCl homeostasis includes a high glomerular filtration rate (GFR, ~180 l/day in humans). Subsequently, nearly all of the filtered fluid and NaCl is reabsorbed along the nephron such that only ~1% of the glomerular filtered amounts are excreted in the urine. As a consequence, GFR and reabsorption have to be coordinated to prevent excessive renal losses of fluid and NaCl. Intrarenal mechanisms that contribute to this coordination from minute to minute include glomerulotubular balance and tubuloglomerular feedback (TGF). According to glomerulotubular balance, an increase in GFR and thus the filtered amounts of NaCl causes a near-proportional increase in NaCl reabsorption in all segments of the tubular and collecting duct system. In absolute amounts, this is particularly evident in the proximal tubule and the medullary and cortical thick ascending limb of Henle (TAL) where the bulk of the filtered NaCl is reabsorbed. The NaCl load at the end of the TAL is sensed, and the TGF establishes an inverse relationship between this tubular NaCl load and the GFR of the same nephron. This stabilizes and limits the NaCl load to the further distal segments, which have a limited capacity to alter NaCl reabsorption from minute to minute, but which, under systemic neurohumoral control, are the site of fine regulation of NaCl balance.

Because urinary fluid and NaCl excretion closely match intake and because variations in fluid and NaCl intake are minor compared with the total amounts filtered, it follows that GFR is the major determinant of renal fluid and NaCl reabsorption. Reabsorption of NaCl requires energy, and the GFR is thus the major determinant of renal O_2 consumption. It follows that GFR is an important determinant of salt balance but also of metabolic aspects of kidney function. Therefore, intrarenal mechanisms that limit GFR when the ratio of renal O_2 supply to demand is significantly reduced could be beneficial. Blood flow to the kidneys amounts to ~20% of cardiac output, and the cortical blood flow, which determines GFR, is also rather high and thus the O_2 supply of the kidney cortex is generous. The situation is quite different, however, in the medulla, where blood flow derives from the postglomerular circulation of the deep cortex. To be able to concentrate the urine, the kidney uses a mechanism that involves a low blood flow to the renal medulla and a counter-current system. As a consequence, the O_2 supply to the renal medulla is low, although active NaCl reabsorption in the medullary TAL is essential for the counter-current system. This situation asks for an intrarenal metabolic control to prevent hypoxic injury in the medulla. Considering on the other hand that cortical blood flow is high but determines via GFR the tubular NaCl load and thus transport work in cortex and medulla, it follows that an intrarenal metabolic control of kidney function requires differential effects on the vasculature and transport systems of cortex and medulla.

Adenosine is a well-studied candidate that participates in intraorgan control mechanisms including acute responses to increased work load (25, 26, 33, 234, 271, 299). The latter increases ATP hydrolysis and adenosine generation. Extracellular adenosine acts on specific G protein-coupled receptors and, in organs like brain, heart, or skeletal muscle, induces vasodilation to match the delivery of O_2 and metabolic fuel to consumption. Additional potential defense mechanisms include a suppression of the release of stimulatory neurotransmitters and a reduction of cell activity (see Fig. 1). The idea of adenosine acting as a "retaliatory metabolite" or as a "homeostatic metabolite" has been reviewed (234, 299). Before this concept can be applied to the kidney and intrarenal

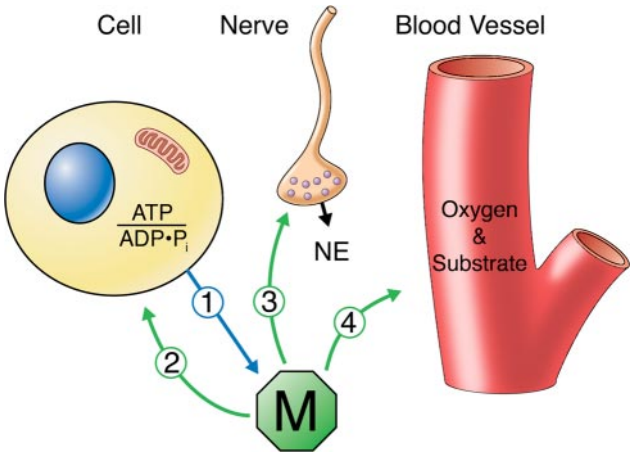

FIG. 1. Schematic illustration of metabolic control of organ function. Mediators of metabolic control (M) are released from cells at a rate that is determined by the phosphorylation potential (ATP/ADP · P_i). The release increases when the phosphorylation potential falls (*1*). The released mediators feed back on the cells to reduce cell activity (*2*), decrease stimulatory neurotransmitter release (*3*), and regulate oxygen and substrate supply to the organ by vasodilation (*4*). NE, norepinephrine.

control mechanisms, it is necessary to understand mechanisms of adenosine formation in the kidney, the effects of adenosine on kidney function, and the determinants of kidney energy consumption and supply.

In this review we examine first the evidence that adenosine is present in the kidney and will be released at an enhanced rate when ATP tissue levels fall (see sect. II), that the kidney expresses specific adenosine membrane receptors (see sect. III), that adenosine mediates actions on renal vascular structures (see sect. IV) and is an element in the TGF response of the nephron (see sect. V), and that adenosine is involved in the regulation of renin secretion (see sect. VI) and transport processes in the tubular and collecting duct system (see sect. VII). Second, we discuss the above findings in a more integrative way in the context of an intrarenal metabolic control of kidney function under physiological conditions (see sect. VIII). Finally, we briefly extend this concept and the role of adenosine in kidney function to aspects of renal pathophysiology, namely, acute renal failure (see sect. IX). The reader is also referred to three relatively recent reviews on the role of adenosine in kidney function (48, 147, 315).

II. ADENOSINE GENERATION IN THE KIDNEY

A. Renal Tissue Content of Adenosine

1. *Normoxia and ischemia*

When rat kidneys were snap frozen, an adenosine tissue content of ~5 nmol/g wet wt was found in normoxic kidneys and the tissue content increased severalfold within a few minutes of renal ischemia (by occlusion of the renal artery) (253). These findings were confirmed and extended to the kidneys of dogs and cats (215). The increase of adenosine tissue content during ischemia preceded the increase of inosine and hypoxanthine, whereas ATP levels were rapidly reduced (245, 253) (see Fig. 2). In vitro studies with suspensions of medullary TAL demonstrated a hypoxia-stimulated adenosine release into the medium. This increase was completely blocked by furosemide or ouabain, indicating that adenosine release is

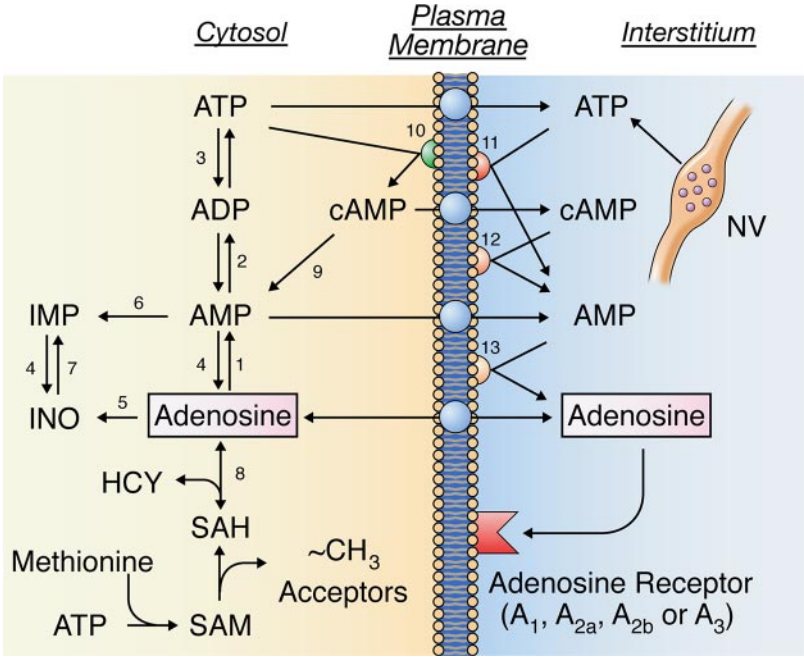

FIG. 2. Pathways and enzymes involved in adenosine formation and metabolism. HCY, homocysteine; IMP, inosine monophosphate; INO, inosine; SAH, *S*-adenosyl-homocysteine; SAM, *S*-adenosyl-methionine. *1*: Adenosine kinase; *2*: adenylyl kinase; *3*: ATPases; *4*: 5′-nucleotidase; *5*: adenosine deaminase; *6*: AMP deaminase; *7*: inosine kinase; *8*: *S*-adenosyl-homocysteine hydrolase; *9*: phosphodiesterase; *10*: adenylyl cyclase; *11*: ecto-ATPases; *12*: ecto-phosphodiesterase; *13*: ecto-5′-nucleotidase. NV, neuronal varicosity.

related to electrolyte transport (21). Thus the kidney makes no exception with respect to enhanced adenosine generation and cellular release following ATP breakdown during oxygen deficiency or enhanced organ work. Further evidence is provided by the renal response to maleic acid and hypertonic saline as outlined in the following section.

2. Maleic acid

ATP depletion without inducing ischemia can be achieved in the kidney by the use of maleic acid. This stereoisomer of fumarate forms a stable complex with coenzyme A, resulting in a fall in ATP levels mainly in the proximal tubules (190, 256, 284). When in rat kidneys ATP levels were reduced by intravenous administration of maleate, adenosine tissue content was increased threefold (245, 247). In dogs, maleate increased adenosine release into renal venous blood and into urine severalfold while leaving arterial adenosine unchanged (10). The changes of kidney function after maleate administration are discussed in section IV.

3. Hypertonic saline

An experimental maneuver to induce a rapid increase in renal transport work that leads to a fall in ATP and an increase of adenosine tissue content is the short time infusion of hypertonic saline into the thoracic aorta (251). This maneuver increases renal NaCl reabsorption because the amount of NaCl filtered significantly increases due to the rise in plasma NaCl concentrations and a concomitant increase in GFR by ~20%. A rise in GFR in response to short time exposure to hypertonic saline (within 10 min) is in accordance with findings of Young and Rostorfer (378). In contrast, prolonged infusion of hypertonic saline directly into the renal artery leads to sustained vasoconstriction that can be blocked by theophylline (94). The results of this experimental series are shown in Figure 3. The experiments demonstrated a reciprocal relationship between the fall in ATP and the increase in adenosine tissue levels depending on the absolute amount of Na^+ reabsorbed by the kidney. Intravenous infusion of hypertonic saline also led to a fall in renal ATP tissue levels, which returned to control levels following furosemide administration (80, 250). The hemodynamic response of the kidney to intra-arterial infusion of hypertonic saline is discussed in section IV.

4. S-adenosylhomocysteine hydrolase binds adenosine

An unsolved issue is the free intracellular adenosine concentration in the kidney. Considering a renal tissue content of adenosine of ~5 nmol/g wet wt (253) and an extracellular adenosine concentration of ~100 nM under normoxic conditions (see sect. II*B*), a calculated cytosolic

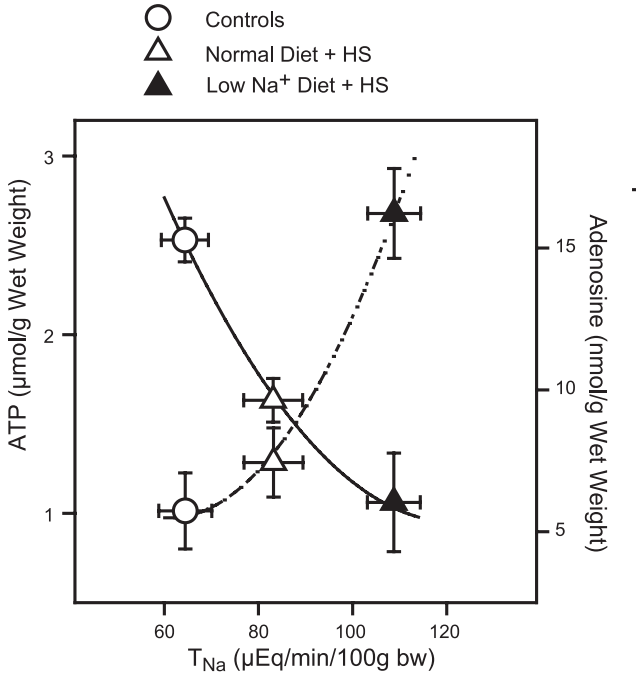

FIG. 3. Inverse changes of kidney contents of ATP (connected with the solid line) and adenosine (dashed line) in response to increasing renal Na^+ reabsorption rate (T_{Na}) by infusion of hypertonic saline (HS) into the thoracic aorta in rats on normal- or low-Na^+ diet. [Adapted from Osswald et al. (251).]

adenosine concentration of 5 μM appears to be unrealistically high. Therefore, one has to assume that >90% of intracellular adenosine is protein bound, which makes it unavailable for deamination by the intracellular enzyme adenosine deaminase (ADA). One candidate protein for binding adenosine intracellularly is the cytosolic enzyme *S*-adenosylhomocysteine (SAH) hydrolase (163, 341) (see Fig. 2). This enzyme hydrolyzes reversibly SAH into adenosine and homocysteine. Two binding sites for adenosine of the SAH hydrolase could be identified, one with high affinity (k_{D1} = 9.2 nM) and one with low affinity (k_{D2} =1.4 μM) (166, 167). Both adenosine binding sites of SAH hydrolase are controlled by the ratio of NAD^+/NADH (162, 163, 165, 166). Based on the intracellular concentration of SAH hydrolase in the kidney of 2.2 μM and its binding capacity, one can calculate that ~20% of intracellular adenosine is bound to SAH hydrolase under normoxic conditions (124, 125, 341). Thus other proteins that can bind intracellular adenosine have to be identified. The formation of SAH in the isolated perfused guinea pig hearts was used by Deussen et al. (63) to calculate that free adenosine concentrations in the cytosol are ~80 nM. Notably, these estimated free cytosolic adenosine concentrations are remarkably similar to the basal adenosine concentrations measured in the kidney interstitium (see below). This may not be unexpected given the presence of equilibrative nucleoside transporters particularly in the

basolateral membranes of kidney tubules (see below) across which adenosine should equilibrate.

In addition to adenosine binding, SAH hydrolase may serve as a target of intracellular adenosine actions (167). Because adenosine inhibits in vitro SAH hydrolase activity in nanomolar concentrations, this action would increase cytosolic SAH levels and thus diminish the methylation potential [the ratio of *S*-adenosylmethionine (SAM) to SAH], which regulates transmethylation reactions in the cell. Moreover, it was shown that renal tissue content of SAH increases severalfold after ischemia (161). In this respect, it is of interest to note that in addition to being expressed in the cytosol of nearly all kidney cells, a prominent staining of SAH hydrolase can be seen in the nuclei of podocytes (164) and that SAH hydrolase accumulates in nuclei of transcriptional activated cells (275). In summary, as in other organs, most of the adenosine content of the kidney is sequestered to intracellular adenosine binding proteins including SAH hydrolase, and much has to be learned about the functional consequences of the interactions between intracellular adenosine and SAH hydrolase.

B. Extracellular Adenosine Concentration

1. Microdialysis technique

With the use of the microdialysis technique in rat kidneys, it was found that mean values of interstitial fluid adenosine concentrations ($[ADO]_{ISF}$) are 55 nM in cortex and 212 nM in medulla (381). Infusion of ATP-$MgCl_2$ resulted in a roughly twofold elevation of adenosine, inosine, hypoxanthine, and uric acid, indicating the capacity of the kidney to metabolize exogenous ATP (381) (see Fig. 2). Employing microdialysis tubes inserted into both kidney cortex and medulla in rats on a normal-NaCl diet, Siragy and Linden (308) found $[ADO]_{ISF}$ in the dialysate from the cortex of 63 nM and from the medulla of 157 nM. Notably, rats consuming a high-NaCl diet had renal cortical and medullary dialysate adenosine concentrations that were increased about sevenfold, whereas low-NaCl diet lowered $[ADO]_{ISF}$ by 64% in both kidney regions compared with normal diet (308). The mechanisms involved are not absolutely clear but may relate to the fact that rats can respond to a high NaCl diet with an increase in GFR (346). As a consequence, absolute and fractional renal NaCl excretion are increased to match increased intake but at the same time the associated increase in GFR enhances absolute renal NaCl reabsorption (primarily in proximal tubule and thick ascending limb)(346), and thus possibly adenosine formation. Further studies are required to clarify this issue. In another study using the microdialysis technique in rabbit kidneys, $[ADO]_{ISF}$ was found to be 293 nM in the cortex under basal conditions and increased threefold after induction of systemic hypoxia (238). In dogs, renal $[ADO]_{ISF}$ was ~117 nM and did not change during reduction of renal perfusion pressure within the autoregulatory range when GFR remained constant (236). One study actually looked at the time course of $[ADO]_{ISF}$ in the effluent of the microdialysis tubes in conscious rats: $[ADO]_{ISF}$ revealed immediately after implantation very high levels that fell subsequently to concentrations between 100 and 200 nM within 2–6 days (237). Although the microdialysis technique may have some limitations, the data show clearly that adenosine is present in the renal interstitium at concentrations sufficient to activate G-coupled adenosine receptors (see sect. III), i.e., in the mid to high nanomolar range under normal-NaCl diet and normoxic conditions with concentrations being about two- to fourfold greater in medulla than in cortex.

2. Sources of extracellular adenosine

To what extent interstitial adenosine is derived from intracellular or from extracellular sources is incompletely understood. It is established that AMP is a major precursor for intracellular and extracellular adenosine formation (see Fig. 2). However, it would be important to know the free concentration of cytosolic AMP and adenosine; the potential efflux rates of ATP, AMP, and adenosine from the cytosol into the interstitium; and the contribution of ecto-5′-nucleotidases to the interstitial adenosine concentration. With the use of the technique of nuclear resonance spectroscopy for ^{31}P phosphorus, it was found in cardiac tissues that free AMP amounts to <5% of total extracted AMP. The measured (96) and calculated (39, 355) concentrations of free AMP in the cytosol of cardiac tissue under normoxic conditions are in the range of 200 nM. These low concentrations are close to the assumed levels of free adenosine in the cytosol (39). Changes in the AMP-adenosine cycle via the activities of cytosolic 5′-nucleotidase and adenosine kinase (see Fig. 2) can lead to significant changes of intracellular adenosine formation (58, 96, 211). The cytosolic 5′-nucleotidase has recently been cloned (for review, see Ref. 138), which should be helpful to further delineate this issue.

A) NUCLEOSIDE TRANSPORTERS. Cellular uptake and release of adenosine is mediated by nucleoside transporters. The nucleoside transporter proteins differentiated so far are divided into five distinct superfamilies that are functionally characterized and vary in substrate specificity. The concentrative nucleoside transporters CNT1-CNT3 [solute carrier (SLC) 28A1–28A3], which mainly localize to the apical membrane of renal epithelium, mediate the intracellular flux of nucleosides. The equilibrative nucleoside transporters ENT1–2 (SLC29A1-SLC29A2), on the other hand, primarily localize to basolateral membranes and mediate bidirectional facilitated diffusion of nucleosides and may thus contribute to cel-

lular adenosine release when cytosolic concentrations increase. However, the knowledge base is far from clear to define satisfactorily how these transporters work, alone or in concert, and under varying intra- and extracellular conditions. Much has to be learned in this regard, and the interested reader is referred to recent reviews on the topic (17, 101, 331).

B) ECTO-5′-NUCLEOTIDASE IN GLOMERULI AND LUMINAL MEMBRANES OF TUBULES. Ecto-5′-nucleotidase is expressed in glomeruli including mesangial cells (45, 134, 189), where it may contribute to the generation of adenosine, which mediates the TGF mechanism (see sect. V). In the first loops of the proximal convoluted tubule, prominent staining of ecto-5′-nucleotidase is visible in the luminal brush-border membrane (56, 91, 112). In the cortical pars recta of the proximal tubule, ecto-5′-nucleotidase staining is low but increases slightly towards the medullary pars recta of the proximal tubule. Also in segments of the distal tubule (intercalated cells), a luminal staining was shown. The luminal localization of ecto-5′-nucleotidase is likely to be involved in the purine salvage pathway of the filtered or luminal released nucleotides that after dephosphorylation can affect luminal adenosine concentrations or be taken up by nucleoside carriers in the brush-border membrane (4, 306). It is, however, unlikely that these luminal ecto-5′-nucleotidase activities produce changes in adenosine concentrations at the basolateral sites of the tubular epithelium and in the interstitium (189, 283).

C) ECTO-5′-NUCLEOTIDASE IN PERITUBULAR SITES. The peritubular staining of ecto-5′-nucleotidase in the kidney has first been attributed to the cells of blood capillaries (112). Le Hir and Kaissling (189), however, demonstrated that the ecto-5′-nucleotidase-positive perivascular cells were in fact fibroblasts. Endothelial cells of the capillaries were negative. The fibroblasts in the interstitium of the kidney make contact with tubular cells and peritubular capillaries and form a sheath around afferent and efferent arterioles of the glomerulus. Under normoxic conditions the ecto-5′-nucleotidase-positive cells are exclusively located in the cortex and cannot be demonstrated in the medulla (56, 91). The intensity of fibroblast staining in the cortex changes in parallel to the increased production of erythropoietin. Under normal conditions, the staining is located predominantly in the deep cortex. The staining increases, however, throughout the whole cortex under challenges of hypobaric oxygen breathing or anemia (189). The exact role of ecto-5′-nucleotidase on the fibroblasts remains to be determined.

D) INTERSTITIAL ATP AS A PRECURSOR OF ADENOSINE. Recently, renal cortical interstitial ATP concentrations assessed by the microdialysis technique in anesthetized dogs were found to be 6.5 nM at a renal artery pressure of 131 mmHg. Stepwise reduction of renal perfusion pressure to 105 and 80 mmHg lowered ATP concentrations to 4.5 and 2.8 nM, respectively. Interstitial adenosine concentrations were 117 nM and remained unaltered by these changes of renal perfusion pressure, which did not affect renal blood flow or GFR (236). A similarly low interstitial ATP/adenosine ratio was reported in the isolated perfused rat heart (203). The 20- to 40-fold higher concentrations of adenosine than those of ATP do not readily support the assumption that this ATP is the major precursor of adenosine in the bulk phase of the interstitial fluid. ATP can serve as a major precursor of adenosine, however, if higher ATP concentrations exist in the unstirred layer at the surface of the plasma membranes, which are equipped with ectoenzymes to metabolize adenine nucleotides (see Fig. 2) and/or the generation of adenosine by these pathways is faster than the downstream adenosine metabolism or cell uptake. Extracellular generation of adenosine from ATP may contribute to the signaling mechanisms of the tubuloglomerular feedback (see sect. V).

E) INTERSTITIAL cAMP AS A PRECURSOR OF ADENOSINE. According to the scheme of Figure 2, extracellular adenosine can be generated from cAMP, which is released by cells of the tubular or vascular system. Jackson and co-workers examined this possibility in several experiments. The cAMP added to the perfusate of isolated perfused kidneys can be converted to AMP by ecto-phosphodiesterases and subsequently to adenosine by ecto-5′-nucleotidases resulting in a release of AMP, adenosine, and inosine into the venous effluent (213). Addition of the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine (IBMX) to the perfusate resulted in an almost complete block of AMP, adenosine, and inosine release. However, when the inhibitor of ecto-5′-nucleotidases, α,β-methylene-adenosine-5′-diphosphate (AMPCP), was infused together with cAMP, the release of AMP was unchanged but adenosine and inosine release were nearly completely inhibited (213). Treating the isolated perfused kidneys with isoproterenol, the endogenously released cAMP is also extracellularly converted to AMP and adenosine yielding a threefold increase of adenosine, inosine, and hypoxanthine (214). The β-blocker propranolol, IBMX, and AMPCP blocked the isoproterenol-induced increase of purines (214). Also in the isolated guinea pig gallbladder, a model of a transporting epithelium, substantial cAMP release into the extracellular space was found after stimulation with prostaglandins (265). Thus the formation of adenosine from extracellular cAMP suggests that adenosine by activation of adenosine A_1 receptors, which can be coupled to an inhibitory G_i protein (see sect. III*D*), can function as a local feedback inhibitor of adenylyl cyclase. This pathway may play a role for effects of adenosine on proximal tubular reabsorption (see sect. VII) as well as adenosine-mediated inhibition of both, renin release (see sect. VI) and vasopressin-stimulated transport in the inner medullary collecting duct (see sect. VII).

C. Renal Excretion of Adenosine

Is the renal adenosine excretion of physiological or pathophysiological significance? Only few data in the literature address this question. Thompson et al. (329) analyzed in anesthetized dogs the renal arterial-venous difference of adenosine and adenosine excretion kinetics following single injections of radiolabeled adenosine into the renal artery (329). Under basal conditions the concentrations of endogenous adenosine in plasma of renal vein and artery were 52–60 nM and not statistically different. Urinary adenosine concentration was 312 nM, and the excretion rate was 0.67 nmol/min. With the use of the single injection method, it was found that 12% of the injected adenosine was recovered in urine and 11% in the renal vein. This low venous recovery was due to cellular uptake by nucleoside transporters as evidenced by a threefold increase of adenosine recovery in the renal vein by the nucleoside transport inhibitor dipyridamole (329). Heyne et al. (127) studied renal adenosine excretion in 12 healthy volunteers under basal conditions, after water loading, and following low and high Na^+ intake. It was found that adenosine excretion (3.2 nmol/min) was independent of urinary flow rate (2–19 ml/min), indicating that passive tubular back-diffusion does not significantly contribute to net adenosine excretion. Moreover, low- and high-Na^+ diet did not change adenosine excretion per milliliter of GFR. These remarkably constant values under normal conditions could provide a basis for the evaluation of renal adenosine excretion as a marker of renal injury in various clinical settings. In fact, enhanced renal adenosine excretion rates were found during renal ischemia (215), maleic acid (10), radiocontrast media application (154), and methotrexate (12).

D. Concluding Remarks

The available data have shown that adenosine is present in the normoxic kidney. The tissue content, ~5 nmol/g wet wt, represents mainly the cytosolic fraction of renal adenosine, whereas only 2–5% of this amount is present in the extracellular compartments, such as tubular fluid/urine and interstitium. Since a calculated cytosolic adenosine concentration of 5 μM appears to be unrealistic, most of the intracellular adenosine must be bound to intracellular proteins including SAH hydrolase. Sources of extracellular adenosine in the kidney include cellular adenosine release as well as extracellular adenosine formation from ATP, AMP, and cAMP being released from the cells. After ATP depletion by ischemia, maleic acid, or hypertonic saline, extracellular adenosine concentrations increase indicating that in the kidney as in other organs adenosine generation is controlled by the phosphorylation potential of the cell. The functional implications are discussed in section VIII.

III. ADENOSINE RECEPTORS IN THE KIDNEY

In recent years, the databases on adenosine receptors, especially on those located in the central nervous system, have intensively grown. The knowledge on the distribution of adenosine receptors in the kidney is less clear, which can be attributed, among other reasons, to low, or, at most, intermediate expression levels in this organ. The concept that adenosine exerts its actions also in the kidney via specific receptors was originally based on binding characteristics or functional experiments using selective pharmacological ligands. Several comprehensive reviews have been published in recent years that focused on adenosine receptors in general or on adenosine receptor subtypes A_1, A_{2a}, A_{2b}, or A_3 (78, 81, 84–86). For nomenclature and classification of the adenosine receptor family, the reader is referred to a recent publication of the International Union of Pharmacology (86). Studies in mice with genetically modified adenosine receptors support the concept that these specific receptors mediate effects of adenosine on the kidney. Currently, all receptor subtypes have been genetically deleted in mouse models except for the adenosine A_{2b} receptor, and some have been overexpressed in selective tissues of transgenic mice. Studies involving these transgenic mice indicated that receptor levels are rate limiting, as effects were amplified upon increases in receptor level (369). This underscores the value of studies on the expression level of adenosine receptors. In this section we review the current knowledge on the distribution and signaling pathways of adenosine receptors in the kidney. The functional aspects of renal adenosine receptors, including observations from knockout-models, are addressed in sections IV–IX.

A. Adenosine A_1 Receptors

With the use of the selective ligands cyclohexyladenosine (CHA) or N^6-*p*-hydroxy-phenyl-isopropyl-adenosine (PIA), adenosine A_1 receptors were first identified by autoradiography in sections of human and guinea pig kidney (257, 358). Moreover, binding sites on glomerular structures for adenosine A_1 receptor ligands were reported in both species (55, 337). Specific binding was more recently reported of ^{3}H-labeled 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), an adenosine A_1 receptor antagonist, to plasma membranes of immortalized cells derived from normal adult human proximal tubule (328). Among the adenosine receptors, the A_1 subtype was the first to be cloned (208). The respective gene, in humans, was allocated to chromosome 1q32.1 (336). Several studies using molecular techniques showed the presence of the adenosine A_1 receptor in the rodent kidney. As depicted in Table 1, adenosine A_1 receptors are present in afferent

TABLE 1. *Expression of adenosine receptors in the kidney*

Receptor Subtype/Localization	Species	Method	References Nos.
Adenosine A_1 receptors			
Whole kidney	Rat	RT-PCR	69, 99, 105, 225, 260, 280
		Northern	313
Whole kidney	Rabbit	Cloning	28
Cortical and medullary membranes	Rat	Western	260, 382
Glomeruli, proximal tubule, mTAL, cTAL, MCD	Rat	RT-PCR	373
Thin limbs of Henle, CD, mTAL	Rat, mouse	RT-PCR	356
Afferent arterioles, mesangial cells, proximal tubules, collecting ducts	Rat	Immunocytochemistry	311
Preglomerular microvessels	Rat	Western/Northern, RT-PCR	150
Glomerular epithelial cells and medullar tubules	Rat	Immunohistochemistry	260
IMCD, JGA slices	Rat	ISH	357
Outer medulla descending vasa recta	Rat	RT-PCR	176
Adenosine A_{2a} receptors			
Whole kidney	Rat	PCR	69, 105, 225, 260
Whole kidney	Guinea pig	Northern	212
Cortical and medullary membranes	Rat	Western	260, 382
Glomerular epithelial cells and capillaries	Rat	Immunohistochemistry	260
Glomeruli	Rat, mouse	RT-PCR	356
Papilla	Rat	ISH	357
OMDVR	Rat	PCR	176
Adenosine A_{2b} receptors			
Whole kidney	Rat	RT-PCR	69, 225, 260
Cortical and medullary membranes	Rat	Western	260, 382
Preglomerular microvessels	Rat	Western/Northern, RT-PCR	150
OMDVR	Rat	RT-PCR	176
cTAL, DCT	Rat, mouse	RT-PCR	356
Baby hamster kidney cells	Hamster	RT-PCR	218
Adenosine A_3 receptors			
Whole kidney	Rat	Cloning/RT-PCR	379
		RT-PCR	69, 200, 225, 260
		Western	260
Whole kidney	Human	RT-PCR	200
		Northern	288
Whole kidney	Sheep	Cloning/RT-PCR	201
		Northern	288
Cortical and medullary membranes	Rat	Western	260, 382

DCT, distal convoluted tubule; cTAL and mTAL, cortical and medullary thick ascending limb of Henle's loop, respectively; IMCD, inner medullary collecting duct; ISH, in situ hybridization; JGA, juxtaglomerular apparatus; MCD, medullary collecting duct; OMDVR, outer medullary descending vasa recta; RT-PCR, reverse transcription-polymerase chain reaction.

arterioles, glomeruli including mesangial cells, juxtaglomerular cells, vasa recta, as well as in various segments of the tubular and collecting duct system including proximal tubule, thin limbs of Henle, TAL, and collecting ducts. In spite of the numerous renal effects of adenosine A_1 receptor activation in humans, data on the localization of this receptor subtype in the human kidney on the molecular level have not been reported so far.

B. Adenosine A_{2a} and A_{2b} Receptors

The adenosine A_2 receptor family consists of two subtypes, the A_{2a} and the A_{2b} receptor, which possess a high and a low agonist affinity, respectively. The adenosine A_2 receptor was first cloned from a canine thyroid cDNA library (196). The human adenosine A_{2a} receptor gene was localized to chromosome 22q11.2 (181, 205). Similar to the adenosine A_1 receptor, renal A_{2a} receptors, so far, have been identified only in rodents (see Table 1). Both the mRNA and the protein of the adenosine A_{2a} receptor were demonstrated in whole kidney preparations. Furthermore, mRNA for the adenosine A_{2a} receptor was detected in the papilla of the rat kidney (357) and in glomeruli of rat and mouse kidney (356). Finally, adenosine A_{2a} receptor mRNA was found in the outer medullary descending vasa recta (176).

Adenosine A_{2b} receptors were first cloned from brain regions of human (272) and rat (282). The responding human gene was localized to chromosome 17p12 (151). There is only sparse information on the presence of adenosine A_{2b} adenosine receptors in the kidney (see Table 1). Adenosine A_{2b} receptor mRNA or protein was detected in whole kidney preparations. In addition, mRNA was detected in the cortical TAL and in the distal convoluted tubule (356) as well as in the outer medullary descending vasa recta (176), and more recently, adenosine A_{2b} receptor mRNA was reported in baby hamster kidney cells (218) and at the protein and mRNA level in rat preglomerular vessels (150).

C. Adenosine A_3 Receptors

The fourth distinct adenosine receptor is the A_3 subtype. It was first cloned from the rat striatum (379). The recombinant striatal adenosine A_3 receptor differs completely compared with the other adenosine subtypes in agonist or antagonist binding. The human adenosine A_3 receptor gene was localized to chromosome 1p (221). Adenosine A_3 receptors have been detected, both on the mRNA and on the protein level, in whole kidney preparations of various species (see Table 1). In contrast, no distinct intrarenal localization has been reported so far. From radioligand binding studies, the presence of the adenosine A_3 receptor in brush-border membranes isolated from pig kidney had been suggested (32). Interestingly, adenosine A_3 receptor mRNA in the kidneys of young rats increased with age from the newborn state to early adolescence by more than one order of magnitude (225).

D. Coupling of Adenosine Receptors

The adenosine receptors belong to the superfamily of G protein coupling receptors. According to a consensus definition, adenosine A_1 receptors induce, via pertussis toxin-sensitive G_i and G_o proteins, adenylyl cyclase inhibition and phospholipase C (PLC) stimulation, whereas adenosine A_{2a} and A_{2b} receptor stimulation leads, via cholera toxin-sensitive stimulatory G proteins, to adenylyl cyclase activation (for detailed information, see reviews in Refs. 79, 85, 86, 88, 229). The adenosine A_3 receptor appears to couple in a similar fashion as A_1 receptors, via inhibitory $G_{q/11}$ protein, to adenylyl cyclase and PLC (for review, see Ref. 86). Thus adenosine receptor subtypes appear to couple to more than one G protein and/or effector system. As outlined in Table 2 for adenosine A_1 and A_2 receptors, the coupling of adenosine receptors to the various effector systems in the kidney is, in general, in agreement with the above-mentioned concepts derived from extrarenal cell types.

E. Concluding Remarks

Each of the family of adenosine receptors has been demonstrated in virtually all organs. In the last years, the knowledge on expression and signal transduction of adenosine receptors in the kidney has grown but is still sparse. In particular, differentiated localization of the adenosine receptors in this organ is incompletely defined. In general, the existing data, however, indicate that the mechanisms of adenosine receptor coupling as obtained from other tissues also apply to the kidney.

TABLE 2. *Effector coupling of adenosine A_1 and A_2 receptors in the kidney*

Type	Effector	Site/Cell	Reference Nos.
		Proximal tubule (PT)	
A_1	AC ↓, cAMP ↓, PKA ↓	Rabbit or rat PT, OKC, LLC-PK_1 cell line, human PT epithelial cell line	41, 42, 53, 191, 326, 328
A_1	PKC ↑	OKC	53, 54
A_2	AC ↑	Isolated tubules of rabbit renal cortex	87
		Thick ascending limb of Henle's loop (TAL)	
A_1	cAMP ↓	Cultured rabbit or rat mTAL, mouse mTAL	19, 40, 335
A_1	G_i, Ca^{2+} ↑	Cultured rabbit mTAL cells	40
A_2	cAMP ↑	Cultured rabbit mTAL, mouse TAL	19,40
		Cortical collecting duct (CCD)	
A_1	cAMP ↓	Cultured rabbit or human CCD	6, 7, 9, 274, 317
A_1	Ca^{2+} ↑, PLC ↑, PKC ↑	Cultured rabbit or human CCD	6, 7, 274, 304, 317
A_2	cAMP ↑	Cultured rabbit or human CCD	9, 274
		Inner medullary collecting duct (IMCD)	
A_1	cAMP ↓	Primary cell culture rat IMCD, perfused rat IMCD, mouse IMCD cell line	73, 226, 371
A_2	cAMP ↓	Primary cell culture rat IMCD	371
		Renal vasculature	
A_1	Ca^{2+} ↑	Isolated, perfused rat kidney	286
A_1	G_i, PLC	Isolated, perfused afferent arterioles	111
A_{2a}	K_{ATP} opening	Afferent arteriole	327
A_{2a}	eNOS activation	Whole kidney	109
		Renin/juxtaglomerular cells	
A_1	Ca^{2+} ↑	Cortical slices	285

AC, adenylyl cyclase; eNOS, endothelial nitric oxide synthase; G_i, inhibitory G protein; mTAL, medullary TAL; OKC, opossum kidney cells; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C.

IV. VASCULAR ACTIONS OF ADENOSINE IN THE KIDNEY

We divide the actions of adenosine on renal vasculature into two different sections, exogenous and endogenous adenosine, for the following reasons: *1*) adenosine injected or infused into the renal artery is reaching all structures of the kidney not taking into account the heterogeneity of its local generation under physiological conditions, *2*) high intra-arterial concentrations of exogenously administered adenosine may activate a variety of endothelial responses like release of prostaglandins or nitric oxide (NO) which may not be induced by increases of endogenous adenosine released into the interstitium, and *3*) the actions of endogenous adenosine being released or formed at an enhanced rate under physiological and pathophysiological conditions, such as an increased metabolic rate or hypoxia, may elicit quite different responses at their receptors compared with the basal state. Renal vascular actions of adenosine have recently been reviewed (110, 240).

A. Exogenous Adenosine

1. *Effects of intrarenal administration of adenosine on renal blood flow and GFR*

Two reports in 1964 described adenosine-induced renal vasoconstriction in the anesthetized dog (333) and in the blood-perfused dog kidney (115), respectively. These findings were confirmed by other investigators (116, 243, 325). Importantly, also conscious dogs respond to intrarenal adenosine injection with vasoconstriction (27). In anesthetized dogs, rats, and cats, intra-arterial single injections of adenosine elicited a renal vasoconstriction, which is rapid in onset and short in duration (243, 252, 319). Continuous intra-arterial infusion of adenosine leads to an initial fall in renal blood flow that lasts, however, for only 1–2 min and then whole renal blood flow returns to or slightly above preinfusion levels. After cessation of adenosine infusion, a short-lasting increase of renal blood flow ("overshoot") can be observed (8, 243, 246, 255, 325) (see Fig. 4). The factors that can modulate the renal response to adenosine are discussed in section IV*D*.

Although whole kidney renal blood flow can return to preinfusion levels within 1–2 min, whole kidney GFR remains to be reduced during steady-state continuous adenosine infusion (255) (see Fig. 4). When micropuncture experiments were performed in rats and dogs, continuous adenosine infusion into the renal artery reduced single-nephron GFR (SNGFR) (derived from superficial nephrons) to a larger extent than whole kidney GFR, indicating that deep-cortical vasodilation counteracts superficial vasoconstriction (103, 254, 255) (see Fig. 4). In fact, adenosine, after an initial vasoconstriction in all cortical zones, induced deep-cortical vasodilation while superficial cortical vasoconstriction persisted (206, 219). The adenosine-induced fall in SNGFR at the kidney surface was the result of afferent arteriolar vasoconstriction with a parallel fall of the hydrostatic pressure in glomerular capillaries and in postglomerular star vessels. Efferent arteriolar dilation did not contribute to the fall in SNGFR (at the applied doses of 0.5 nmol · min^{-1} · ml renal blood $flow^{-1}$) (103, 255). Other investigators employing intrarenal infusion of adenosine in the rat at four- to fivefold higher doses did not observe significant changes in whole kidney GFR (83, 219). The reasons for these discrepancies can be due to *1*) differences in the routes and doses of infused adenosine which can lead to activation of different adenosine receptors (see below) or *2*) differences in the Na^+ and volume status of the animals which is known to modulate the renal vascular response to adenosine (see sect. IV*D1*).

A different approach of intrarenal adenosine administration was chosen by Pawlowska et al. (261) who infused adenosine into the renal interstitial space of rats via implanted capsules. The data clearly demonstrated that adenosine and two stable analogs, 2-chloro-adenosine and NECA, decreased GFR by 50–80% while leaving total renal blood flow unchanged (261). To analyze the intrarenal blood flow distribution during interstitial adenosine

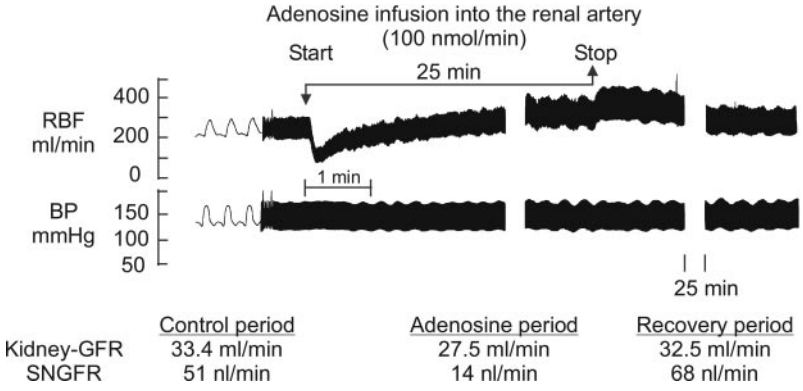

FIG. 4. Renal blood flow (RBF) response to adenosine infusion into the renal artery in anesthetized dogs. Original tracing of RBF in a dog subjected to micropuncture. Measurements of whole kidney and single-nephron glomerular filtration rate (SNGFR) were performed during steady-state of continuous adenosine infusion for 25 min. Whereas RBF normalizes within minutes, kidney GFR and particularly SNGFR in superficial nephrons remain reduced. [Adapted from Osswald et al. (255).]

infusion, Laser-Doppler flow probes were used to assess medullary and cortical blood flow in rat kidneys. Cortical blood flow was reduced by adenosine infusion for 1 min while medullary blood flow increased above preinfusion levels after an initial short-lasting decrease. The adenosine A_1 receptor agonist CPA reduced flow in both regions, whereas the specific adenosine A_2 receptor agonist CGS-21680C increased medullary blood flow to 1.8-fold above baseline (2). When adenosine was infused directly into the medullary interstitium, outer and inner medullary blood flow were increased together with urine and Na^+ excretion, a response that was sensitive to the adenosine A_2 receptor antagonist 3,7-dimethyl-1-propargylxanthine (DMPX) (381).

Studies in the isolated in vitro perfused outer medullary descending vasa recta (OMDVR) revealed that abluminal adenosine application causes vasoconstriction at low concentrations (10 pM to 0.1 μM), whereas high concentrations (1–10 μM) reversed the vasoconstriction (307). These vessels of the OMDVR are equipped with adenosine A_1 and A_{2a}/A_{2b} receptors (176) consistent with the notion that low adenosine concentrations caused vasoconstriction via the adenosine A_1 receptors, whereas higher concentrations can vasodilate via adenosine A_2 receptors.

2. *Adenosine effects on pre- and postglomerular arteries*

Direct videometric assessment of the vascular reactivity of pre- and postglomerular arteries can be achieved using the "split-hydronephrotic" kidney technique. In this experimental model adenosine induced a preglomerular constriction, when applied topically from the interstitial side, which was most prominent in the distal part of the afferent arterioles (64). With the use of adenosine agonists and antagonists with different receptor subtype specificity, the data supported the concept that activation of adenosine A_1 receptors leads to constriction mainly of afferent arterioles near the glomerulus, whereas adenosine A_2 receptor activation leads to dilation mainly of the postglomerular arteries (65, 90, 133). Another study in the isolated perfused hydronephrotic rat kidney preparation provided evidence for both adenosine-induced constriction and dilation of afferent arterioles, and these effects were dependent on activation of adenosine A_1 and A_{2a}/A_{2b} receptors, respectively (327).

Experiments in isolated perfused rabbit afferent arterioles indicated an essentially exclusive presence of adenosine A_1 receptors in the glomerular entrance segment of the afferent arteriole, whereas in more proximal regions adenosine A_2 receptors appear to be expressed in low density (359). Notably, studies in rat juxtamedullary afferent arterioles using the in vitro blood-perfused juxtamedullary nephron technique revealed that the metabolically stable adenosine analog 2-chloroadenosine reduced the vessel diameter at a concentration of 1 μM, whereas at 100 μM afferent vasodilation was observed (140, 141). Similarly, studies in the blood-perfused rat juxtamedullary nephron preparation also indicated the presence of adenosine A_1 and A_{2a} receptors on afferent and efferent arterioles of juxtamedullary nephrons, such that adenosine A_{2a} receptor-mediated vasodilation partially buffers adenosine-induced vasoconstriction in both pre- and postglomerular segments of the renal microvasculature (235). In comparison, isolated-perfused afferent arterioles from superficial cortex of rabbit kidneys constricted in a dose-dependent manner when exposed to adenosine added to either lumen or bath. Adenosine A_1 receptor antagonists blocked this adenosine effect. Higher micromolar concentrations of adenosine added to either lumen or bath only induced vasodilation in the presence of an adenosine A_1 receptor antagonist. This effect was blocked by an adenosine A_2 receptor antagonist (376). These data indicate that adenosine A_1 receptor-mediated afferent arteriolar constriction may dominate in superficial nephrons, whereas juxtamedullary or deep cortical nephrons can respond to high adenosine concentrations with adenosine A_2 receptor-mediated vasodilation. This would be consistent with persistent superficial cortical vasoconstriction and deep cortical vasodilation in response to adenosine infusion (see above).

3. *Adenosine actions on human kidneys*

Edlund and Sollevi (72) infused adenosine intravenously in eight healthy awake volunteers in doses of 60–80 $\mu g \cdot kg^{-1} \cdot min^{-1}$. GFR was lowered by 28% while blood pressure and renal blood flow were unchanged. As a result of systemic vasodilation, heart rate and plasma concentrations of epinephrine and norepinephrine were increased while total peripheral resistance was decreased. Plasma renin activity was unchanged despite the activation of the efferent sympathetic tone (72) (see sect. VI). Similar results were reported by Balakrishnan et al. (16). In a subsequent study, adenosine was directly infused into the renal artery of volunteers at a dose of 2–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, i.e., nearly the same dose applied in the dog experiments depicted in Figure 4. The infusion of adenosine reduced GFR significantly in the volunteers and tended to increase renal blood flow determined by *p*-aminohippurate (PAH) clearance (71). For comparison, 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ adenosine infused into the renal vein induced no systemic effects on the cardiovascular system or on plasma catecholamines, indicating that intra-arterial adenosine infusion is unlikely to change renal function by systemic responses. Moreover, single injections of adenosine into the renal artery at doses between 0.01 and 1,000 μg adenosine (dissolved in 1 ml saline) induced a rapid fall in renal blood flow, as measured by an intravascular

catheter connected to Doppler flowmetry, which, similar to the experiments in dog (243), returned to preinjection levels within 5–30 s (209). Thus the renal hemodynamic response to injections or infusions of adenosine is very similar in dogs and humans.

B. Endogenous Adenosine

1. Postocclusive ischemia

The interruption of arterial blood supply to an organ and the observation of postocclusive flow patterns are used as methods to study the relationship between energy metabolism and blood flow regulation (26). In organs like heart, brain, and skeletal muscle, a postocclusive hyperemia was observed (26). More than a century ago it was found that the kidney makes an exception compared with other organs as the reperfusion following a release of an artery clamp was virtually absent (31). Direct measurements of renal blood flow in rats demonstrated that in the kidney the postocclusive blood flow pattern is characterized by a short-lasting vasoconstriction (253). Because adenosine tissue content increases within 30 s of ischemia threefold and because theophylline, in doses which can antagonize exogenously applied adenosine, also blocked the postocclusive vasoconstriction, we concluded that endogenous adenosine was responsible for this unique vascular response (253). A typical tracing from this type of experiments is shown in Figure 5.

A postocclusive vasoconstriction was also found in isolated perfused kidneys. Inhibition of 5′-nucleotidase or blocking of adenosine A_1 receptors abolished the hypoxia-induced increase of perfusion pressure, supporting the assumption that hypoxia induces an increase in adenosine formation in the kidney that leads to vasoconstriction via activation of adenosine A_1 receptors (276). In cats, the postocclusive flow pattern could be changed into a strong postocclusive vasoconstriction by meclofenamate, a cyclooxygenase inhibitor, indicating a protective effect of prostaglandins in the kidney against the vasoconstrictive action of intrarenal accumulating adenosine (319). With the use of the specific adenosine A_1 receptor antagonist DPCPX, the postocclusive vasoconstriction could be reduced up to complete blockade in a dose-dependent manner (270). These data indicate that endogenous adenosine accumulating in the kidney induces via adenosine A_1 receptor activation the renal vasoconstriction seen after the release of a short-lasting renal artery clamp (see also sect. IX).

2. Hypertonic saline infusion

As illustrated in part in Figure 3, measurements of ATP, ADP, and AMP in the rat kidney with and without hypertonic saline infusion into the thoracic aorta revealed that the increased renal work load by hypertonic saline led to a fall of renal ATP and the energy charge (171, 250) associated with a threefold increase in renal adenosine levels (251). The renal vasculature responded to prolonged hypertonic saline infusion into the renal artery with sustained vasoconstriction, and the renin secretion was reduced to virtually zero (93). In subsequent studies it was shown that theophylline could block both vasoconstriction and suppression of renin release (94, 318). Using a nonxanthine adenosine receptor antagonist, CGS 15934 A, which is devoid of inhibitory action on phosphodiesterases (368), Callis et al. (43) could antagonize in anesthetized dogs the hypertonic saline-induced renal vasoconstriction. Several studies confirmed the observation of sustained renal vasoconstriction due to hypertonic saline and supported the assumption that adenosine is mediating this response (62, 92, 202). Micropuncture experiments revealed that acute hypernatriemia decreases SNGFR measured by distal collection (with intact flow at the macula densa), whereas SNGFR from proximal collections (with interruption of flow to the macula densa) was increased, indicating that the TGF mechanism was responsible for the fall in GFR during hypernatriemia

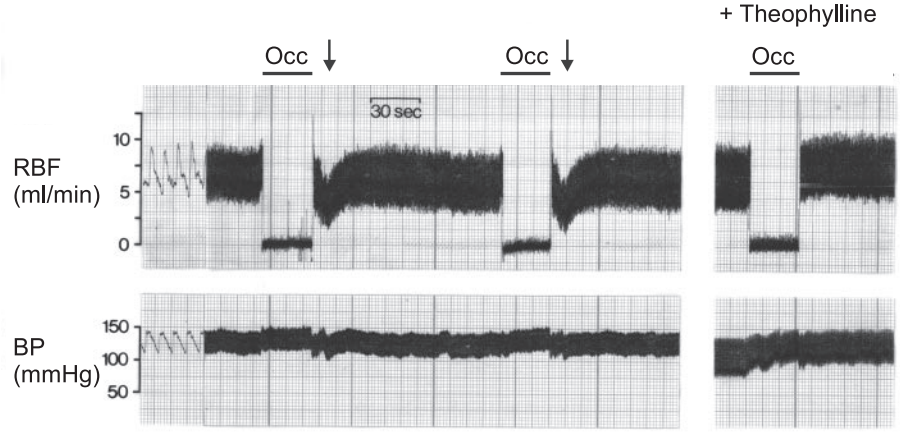

FIG. 5. Postocclusive reduction (arrow) of renal blood flow (RBF) in the rat. Administration of the unselective adenosine receptor antagonist theophylline (3.3 μmol/100 g body wt iv) abolished the postocclusive RBF reduction, suggesting that this response is mediated by adenosine accumulating in the kidney during the occlusion of the renal artery. Occ, renal artery occlusion; BP, blood pressure. [Adapted from Osswald et al. (253).]

(291). Taken together, hypertonic saline infusion leads to an increase of the tubular Na^+ load to which the kidney responds with *1*) a fall in ATP, *2*) an increase in adenosine tissue levels, *3*) sustained renal vasoconstriction due to TGF activation, and *4*) reduced rate of renin secretion. The latter two effects are sensitive to adenosine receptor antagonism. The role of adenosine in renin release is outlined in section VI.

3. Maleic acid

As discussed in section II*A2*, maleic acid lowers ATP and increases adenosine levels in the kidney (245, 247). This maleate action is associated with transport inhibition mainly in the proximal tubule (e.g., glucose, amino acids, bicarbonate, and phosphate). As a consequence, maleate reduced SNGFR in the rat kidney by 42% due to a rise in proximal tubular hydrostatic pressure and activation of TGF (190). A role for TGF was indicated by the finding that the ratio of proximal to distal measurements of SNGFR, i.e., without and with intact flow at the macula densa, was significantly increased by maleate. However, maleate also reduced SNGFR from proximal tubular collections, i.e., without intact flow at the macula densa, pointing to a TGF-independent component of SNGFR reduction in response to maleate. The adenosine receptor antagonist theophylline can attenuate the fall in GFR in response to maleate by ~50% (247). Similar results were obtained in dogs (10). These data indicate that endogenous adenosine mediates, at least in part, the reduction of GFR in response to maleate, possibly by activating TGF as well as by adenosine-induced vasoconstriction outside the TGF pathway. The role of adenosine in TGF is outlined in section V.

4. Application of adenosine receptor antagonists

Application of receptor antagonists can provide information on the ambient activity of the system inhibited. In healthy, male subjects oral application of the adenosine A_1 receptor antagonist FK-453 significantly increased GFR by ~20% (determined by clearance of ^{51}Cr-labeled EDTA after 2 and 3 h). FK-453 tended to increase effective renal plasma flow (determined by clearance of ^{125}I-hippuran) without significant changes in mean arterial blood pressure (15). These data suggest that endogenous adenosine through activation of adenosine A_1 receptors elicits a tonic suppression of GFR. This suppression may reflect at least in part the tonic influence of TGF on GFR as adenosine through activation of adenosine A_1 receptors mediates TGF-induced afferent arteriolar constriction (see sect. V). In comparison, no effect on GFR could be observed in response to the adenosine A_3 receptor antagonists MRS-1191 and MRS-1220 in the rat (227).

Infusion of the adenosine A_1 receptor antagonist DPCPX into the renal medulla of rats did not change medullary blood flow, while the selective adenosine A_2 receptor antagonist DMPX decreased medullary flow (381). In accordance, renal interstitial infusion of the specific adenosine A_2 receptor agonist CGS-21680C in rats increased medullary blood flow to 1.8-fold above baseline (2). These data suggest that endogenous adenosine at physiological concentrations dilates medullary vessels via adenosine A_2 receptors.

C. Mechanisms of Adenosine-Mediated Vasoconstriction and Vasodilation

To further elucidate the signaling mechanisms involved in adenosine-mediated vasoconstriction, Hansen et al. (111) performed studies in perfused afferent arterioles from mouse kidney. They observed that adenosine, when added to the bath, caused constriction in the concentration range of 10^{-9} to 10^{-6} M. Adenosine-induced vasoconstriction was stable for up to 30 min and was most pronounced in the most distal part of the afferent arterioles. Adenosine did not cause vasoconstriction in arterioles from mice lacking adenosine A_1 receptors confirming a role of this receptor in adenosine-mediated vasoconstriction in the kidney. Further studies indicated that the constriction response to adenosine in afferent arterioles is mediated by adenosine A_1 receptors coupled to a pertussis toxin-sensitive G_i protein and subsequent activation of PLC, presumably through $\beta\gamma$-subunits released from $G\alpha_i$ (111). Similarly, studies in the isolated perfused rat kidney indicated a pertussis toxin-sensitive step between the occupation of adenosine A_1 receptors on renal vascular smooth muscle cells and vasoconstriction induced by increased Ca^{2+} influx through potential-operated Ca^{2+} channels (286). With regard to adenosine-induced renal vasodilation, a study using an isolated-perfused hydronephrotic rat kidney preparation showed that adenosine-induced dilation of afferent arterioles was mediated by adenosine A_{2a} receptor-dependent activation of K_{ATP} channels (327). A recent study in mice using intravenous infusion of adenosine indicated that the resulting renal vasodilation is due to adenosine A_{2a} receptor-mediated activation of endothelial NO synthase (109). Whether the same pathway contributes to medullary vasodilation in response to endogenous adenosine, which probably derives from the abluminal site, remains to be determined.

D. Factors That Modulate the Vascular Response to Adenosine

1. Dietary NaCl status and renin-angiotensin system

One prominent factor that modulates the renal response to low doses of adenosine is the NaCl diet through

activation of the renin-angiotensin system. In rats and dogs, the kidney is rendered insensitive to the vasoconstrictive action of adenosine at conditions of a high NaCl diet and volume expansion when plasma renin activity is low (11, 249, 252, 254). Correspondingly, high renin states of the animal are associated with an increased potency of adenosine to induce vasoconstriction and to lower GFR (249, 252, 254). The vasoconstrictive action of exogenous and endogenous adenosine can be antagonized by angiotensin II receptor antagonists (64, 207, 249, 320). Likewise, inhibitors of angiotensin I converting enzyme can block adenosine-induced renal vasoconstriction (65). The assumed interaction of angiotensin II and adenosine in preglomerular vessels was confirmed in dogs (106, 107). More detailed studies employing micropuncture experiments in the rat and in isolated perfused afferent arterioles from rabbits revealed a mutual dependency and cooperation of adenosine and angiotensin II in producing afferent arteriolar constriction (360). Further evidence for this conclusion was provided by the observation that angiotensin II AT_1 receptor knockout mice show a markedly reduced vasoconstrictor response to the specific adenosine A_1 receptor agonist CHA (338). Vice versa, deficiency of adenosine A_1 receptors diminishes the effectiveness of angiotensin II to constrict afferent arterioles and to reduce GFR (108). The cellular mechanisms involved in this mutual dependency and cooperation remain to be determined.

2. Renal artery pressure and prostaglandins

A reduction of renal perfusion pressure to 65–70 mmHg by clamping the aorta above the origin of the renal arteries nearly abolishes adenosine-induced vasoconstriction in dogs and rats (103, 210). In rats, administration of indomethacin to inhibit prostaglandin synthesis can restore the adenosine-induced vasoconstriction under these conditions (103) and was shown to potentiate the vasoconstrictive action of endogenous and exogenous adenosine (268). Similarly, a 100-fold increase in sensitivity to vasoconstriction induced by single injections of adenosine into the renal artery of cat kidneys was achieved by pretreatment of the animals with meclofenamate (319). These data indicate that prostaglandins counteract adenosine-induced renal vasoconstriction. Adenosine-induced vasodilation, mainly in the deep cortex, however, is not sensitive to inhibitors of the cyclooxygenase (2, 316).

3. Inhibitors of NO synthase

Another system that counteracts the vasoconstrictive action of many autacoids of the kidney is the production of NO by different NO synthases (NOS) in the kidney. After administration of unselective NOS inhibitors like N^{ω}-nitro-L-arginine, the sensitivity of the kidney to the vasoconstrictive action of adenosine is enhanced at least 10-fold (18, 269). This is consistent with the finding that adenosine infusion-induced vasodilation via adenosine A_{2a} receptors is mediated by activation of endothelial NOS (109).

4. Renal nerves

In virtually all organs, adenosine inhibits the transmitter release from nerve endings by activation of presynaptic adenosine A_1 receptors. This inhibition may involve regulation of the Ca^{2+} influx via voltage-dependent calcium channels and hyperpolarization of the presynaptic nerve terminal (for review, see Ref. 70). In the kidney, adenosine can inhibit stimulation-evoked norepinephrine overflow, but it was also found to potentiate the postsynaptic norepinephrine-induced vasoconstriction (120, 121). Thus the numerous observations on the interactions between adenosine and the firing rate of nerve endings most likely apply also to the kidney.

5. Insulin-dependent diabetes mellitus

Renal function in early insulin-dependent diabetes mellitus (IDDM) is characterized by glomerular hyperfiltration. The hypothesis was brought forward that a deficiency of intrarenal vasoconstrictive mechanisms contributes to the observed hyperfiltration (347). Therefore, dipyridamole, an adenosine reuptake inhibitor, was administered to rats with streptozotocin-induced IDDM for 4 wk. Thereafter, micropuncture experiments were performed to assess renal function and TGF activity. It was found that dipyridamole restored IDDM-induced attenuation of TGF activity, normalized glomerular hyperfiltration, and reduced proteinuria by 60% (347). These results are in accordance with the hypothesis that local adenosine concentrations at and around the afferent arterioles might be reduced in early diabetes [possibly as a consequence of primary tubular hyperreabsorption and a resulting low TGF signal at the macula densa (344)] and contribute to glomerular hyperfiltration in the early diabetic kidney. Furthermore, the renal vasculature of diabetic rats exhibited a 30-fold higher sensitivity to endogenously released and to exogenously administered adenosine when compared with nondiabetic control rats (270). These findings may indicate low extracellular adenosine concentrations and a secondary upregulation of adenosine A_1 receptors in afferent arterioles in early diabetes mellitus. This initial finding was confirmed and extended by showing that NOS inhibitors potentiated the adenosine-induced vasoconstriction in control rats to a much greater extent than in IDDM rats (269). Similarly, inhibition of cyclooxygenase by indomethacin enhanced the vasoconstrictive potency of exogenous and endogenous adenosine in control rats but not in diabetic rats (268). Interestingly, in rats with streptozotocin-induced IDDM, adenosine A_1 receptor protein expression was increased in membranes of the medulla, whereas adenosine A_{2a} receptor protein expression was increased in membranes and cytosolic fractions of the cor-

tex (260). The implications of these findings are unclear, but the changes could be functionally relevant since studies involving mice overexpressing adenosine receptors indicated that receptor levels are rate limiting for adenosine actions (369). Clearly, more studies are required to elucidate the role of adenosine in the diabetic kidney. Table 3 summarizes further interactions between different conditions, drugs, and hormones and the renal vasoconstriction mediated by adenosine.

E. Concluding Remarks

Adenosine can induce both vasoconstriction and vasodilation in the kidney under in vivo and in vitro conditions. Adenosine-induced sustained vasoconstriction via adenosine A_1 receptor activation is predominant in the outer cortex by increasing the resistance of afferent arterioles and lowering GFR. In the deep cortex and medulla, adenosine-induced vasodilation via adenosine A_2 receptor activation is associated with an increase of medullary blood flow and thus medullary oxygenation. The functional implications of this heterogeneous response of the renal vasculature to adenosine are discussed in section VIII. Experiments with hypertonic saline infusion and maleate application suggested that a modest general rise in renal tissue adenosine content has little vasoconstrictive effect, supporting the importance of adenosine locally derived from the juxtaglomerular apparatus in the control of afferent arteriolar tone. This is outlined in more detail in the next section.

V. ADENOSINE AND TUBULOGLOMERULAR FEEDBACK

A. Tubuloglomerular Feedback

The TGF mechanism refers to a series of events whereby changes in the Na^+, Cl^-, and K^+ concentrations ([Na-Cl-K]) in the tubular fluid at the end of the TAL are sensed by the macula densa, which then elicits a twofold response in the juxtaglomerular apparatus (JGA): *1*) a change in SNGFR by altering the vascular tone predominantly in the afferent arteriole and *2*) an alteration of renin secretion from granular cells (for review, see Ref. 294). While an increase in late proximal tubular flow rate, which increases the respective electrolyte concentrations at the macula densa, lowers both SNGFR and renin secretion, a reduction in late proximal tubular flow rate elicits the opposite effects. In the following the role of adenosine in TGF-mediated control of SNGFR is outlined. The effect of adenosine on renin secretion is discussed in section VI.

The TGF mechanism, which operates locally on the single-nephron level, adjusts afferent arteriolar resistance and SNGFR in response to changes in early distal tubular NaCl concentrations to keep the fluid and NaCl delivery to the distal nephron within certain limits. A relative constant load to the distal nephron seems necessary in order for this part of the nephron to accomplish the fine adjustments in absolute reabsorption to meet body needs. In this regard, the TGF mechanism serves to establish an appropriate balance between GFR and the reabsorption in proximal tubule and loop of Henle. The importance of the symmetry between nephron filtration and reabsorption can be appreciated from the fact that a disparity of as little as 5% between filtered load and the reabsorption rate would lead to a net loss of about one-third of the total extracellular fluid volume within 1 day, a situation which inevitably would lead to vascular collapse. Under conditions of minor changes in reabsorption in proximal tubule and loop of Henle, by adjusting afferent arteriolar resistance and SNGFR to keep early distal tubular fluid and NaCl delivery constant, the TGF mechanism also contributes to autoregulation of GFR. Because the amount of fluid and NaCl filtered in the glomeruli is an important determinant of reabsorption and thus of energy demand

TABLE 3. *Parallel response of adenosine-induced vasoconstriction and tubuloglomerular feedback activity to a number of different experimental conditions, drugs, and hormones*

	ADO-Induced Vasoconstriction	TGF Activity	Reference Nos.	
			ADO	TGF
Conditions				
Low-salt diet, volume depletion, or hemorrhage	Potentiation	↑	252, 254	155, 222, 223, 305
High-salt diet or volume expansion	Attenuation	↓	252 ,254	263
Drugs/hormones				
Theophylline or ADO A_1 antagonists	Inhibition	↓	243	249, 251, 289, 298, 330
Calcium antagonists	Inhibition	↓	8	44, 217, 233
Angiotensin II blockade	Inhibition	↓	107,249,320	364
NOS inhibition	Potentiation	↑	269	145, 332, 350, 351, 365
ADO reuptake ↓	Potentiation	↑	11, 244	249, 251, 347
Angiotensin II	Potentiation	↑	106, 360	135, 216, 273, 290, 292, 293

NOS, nitric oxide synthase; ADO, adenosine; TGF, tubuloglomerular feedback.

in the tubular and collecting duct system, the TGF mechanism by affecting GFR contributes to the metabolic control of kidney function.

The TGF mechanism can be divided into three steps: *1*) the luminal signal in the tubular fluid is sensed by the macula densa, *2*) signal transduction by the macula densa/extraglomerular mesangium to generate factors that *3*) ultimately exert effects at the afferent arterioles including vascular smooth muscle cells and renin-containing cells (see also Fig. 7). There is agreement that the luminal signal is primarily recognized by the Na^+-$2Cl^-$-K^+ cotransporter, which is located in the luminal membrane of macula densa cells. By which mechanism the macula densa cells process this signal, however, is not fully understood.

Various factors have been suggested to be involved in signal transmission of the TGF response. What would be the functional requirements for a factor to mediate these minute-to-minute responses? First, the factor must have a rapid onset of action within seconds, since the change in vascular tone following an increase of luminal electrolyte concentration in the tubular fluid at the macula densa occurs with a short delay of a few seconds (132). Second, the duration of the vascular response has to be short and must be fully reversible within seconds. Third, the factor must be generated locally in the JGA, since other nephrons in close proximity to the perfused nephron do not respond to the stimulus provided the blood supply originates from a different cortical radial artery (104, 131, 224). Fourth, the factor must be generated or released in dependence of Na^+-$2Cl^-$-K^+ cotransport at the macula densa. Furthermore, substances acting synergistic to the factor should enhance the TGF response, whereas substances acting antagonistic to the factor should be inhibitory. Because the TGF response includes also an inhibition of renin secretion following elevated NaCl concentration at the macula densa, the factor may also have an inhibitory action on renin release, but this is not absolutely critical, since macula densa-dependent regulation of GFR and renin may be caused by different mechanisms. As outlined in the following, experimental evidence has been provided that adenosine fulfills the above criteria.

B. Altering TGF Responses by Manipulating Adenosine Receptor Activation or Adenosine Formation

Adenosine may contribute to signal transduction in TGF because it reduces glomerular capillary pressure and SNGFR by predominant afferent arteriolar vasoconstriction and because this response is rapid in onset and short in duration when the adenosine delivery is discontinued (11, 103, 133, 228, 244, 249, 251, 255, 289, 298). Table 3 summarizes the interactions between different conditions and factors and the renal vasoconstriction mediated by adenosine as well as TGF activity. Furthermore, adenosine inhibits renin release even at concentrations that are well below those inducing vasoconstriction (8, 10, 144, 249, 254, 314, 361)(see sect. VI). Most importantly, using adenosine receptor antagonists or maneuvers that lower adenosine concentrations, it is possible to inhibit the TGF response of the nephron. As shown in micropuncture experiments in anesthetized rats, the unselective adenosine receptor blocker theophylline, applied in a dose that antagonizes the renal vasoconstriction in response to exogenous adenosine, also blocks the TGF-induced fall in early proximal tubular flow rate or stop flow pressure (SFP) as surrogates for SNGFR or glomerular capillary pressure, respectively (251, 297). A similar inhibition of TGF was observed with the unselective adenosine receptor blocker PSPX (82).

Suggesting a predominant role of adenosine A_1 receptors in macula densa control of SNGFR and glomerular capillary pressure, micropuncture studies in rats revealed *1*) that intraluminal (82) or peritubular (298) infusion of adenosine A_1-selective agonists reduce SFP and *2*) that the selective adenosine A_1 receptor antagonists DPCPX, KW-3902, or CVT-124 inhibit the TGF-induced fall in SFP or SNGFR (157, 298, 366). Moreover, it was observed in the isolated-perfused rabbit JGA that the adenosine A_1 receptor antagonist FK-838 completely prevented afferent arteriolar vasoconstriction in response to increasing the NaCl concentration in the macula densa perfusate (277). In accordance, experiments in free-flowing rat nephrons demonstrated that the ability of TGF to compensate for small perturbations in ambient tubular flow was reduced by intraluminal application of the lipophilic adenosine A_1 receptor antagonist KW-3902 (330).

With the manipulation of local adenosine formation, it was observed that infusion of the adenosine deaminase inhibitor erythro-9-(2-hydroxy-3-nonyl)adenine, which is supposed to reduce adenosine degradation, potentiated the TGF response (249). Similarly, dipyridamole, which inhibits cellular adenosine uptake and thus elevates extracellular adenosine levels, potentiated the maximum TGF response (251). With regard to aspects of pathophysiology, it has been shown that the activity of TGF is reduced in early experimental diabetes mellitus (343, 347). In the latter condition, chronic dipyridamole treatment not only normalized maximum TGF responses but also prevented glomerular hyperfiltration and lowered proteinuria (347). However, inhibitors of nucleoside transporters could also inhibit TGF by increasing extracellular adenosine concentrations to levels that activate vasodilatory adenosine A_2 receptors in the afferent arteriole (156, 327) and/or by possibly reducing the release of adenosine from macula densa cells (see below). Thus the effect of this kind of agent on TGF is not predictable. In contrast to the outlined experiments with dipyridamole, infusion of adenosine deaminase, which is supposed to

degrade adenosine and thus lower extracellular adenosine concentrations, attenuated the TGF-mediated fall in SFP (249). Similarly, luminal application of the 5′-nucleotidase inhibitor α,β-methyleneadenosine-5′-diphosphate (AMPCP), which inhibits the conversion of AMP to adenosine, was found to reduce the ability of TGF to compensate for small free-flow perturbations in ambient proximal tubular flow. The 5′-nucleotidase inhibitor in addition reduced *1*) the maximum fall in SNGFR during increasing perfusion of Henle's loop from 4 to 37 nl/min, i.e., in response to increasing [Na-Cl-K] at the macula densa from low to high, and *2*) the slope of the TGF curve at the natural flow rate (330). In accordance, in experiments in which rabbit afferent arterioles and attached macula densas were simultaneously microperfused in vitro, it was confirmed that AMPCP blocks the TGF response (279). Thus maneuvers that lower local adenosine concentrations also reduce TGF responses and maneuvers that increase local adenosine concentrations enhance TGF responses.

C. Absence of TGF Response in Adenosine A_1 Receptor-Deficient Mice and Consequences on the Single-Nephron Level

In 2001 two groups investigated the role of adenosine A_1 receptors in TGF response by generating independently knockout mice for the adenosine A_1 receptor (see Fig. 6, *A* and *B*). Sun et al. (322) observed that the TGF response assessed as the fall in SFP or early proximal flow rate during an increase in loop of Henle perfusion from 0 to 30 nl/min was completely absent in adenosine A_1 receptor knockout mice. Similarly, Brown et al. (38) showed that the TGF response was abolished in adenosine A_1 receptor knockout mice when assessed as the fall in SFP during perfusion of Henle's loop at 0 and 35 nl/min. Moreover, a more recent study demonstrated that acutely lowering the NaCl concentration at the macula densa from normal to minimal levels (by collecting tubular fluid first from distal and then from proximal tubular sites) increased SNGFR only in wild-type but not in adenosine A_1 receptor knockout mice. These results indicate a tonic, SNGFR-depressing effect of the NaCl concentration at the macula densa that depends on intact adenosine A_1 receptors (348). Presumably related to the absence of TGF regulation, autoregulation of renal vascular resistance is reduced in adenosine A_1 receptor knockout mice (117).

Within the same nephron, proximal tubular hydrostatic pressure (P_{PT}) and flow rate, as well as distal tubular Cl^- concentration, can exhibit spontaneous oscillations of the same frequency but with a phase lag as first reported by Holstein-Rathlou and Marsh in rats (132). As suggested originally by Leyssac and co-workers (192, 193), these oscillations are caused by the operation of TGF. Consistent with this notion, spontaneous oscillations in P_{PT} were observed in wild-type mice but were absent in mice lacking adenosine A_1 receptors (348). Using mathematical modeling, Layton et al. (180) proposed that the spontaneous oscillations reduce the regulatory ability of TGF and that this will enhance distal Na^+ delivery and renal Na^+ excretion. Further studies in adenosine A_1 receptor knockout mice lacking spontaneous oscillations may help to clarify the role of these spontaneous oscillations in Na^+ homeostasis and blood pressure regulation (see also sect. VIII).

An increase in proximal tubular flow rate is expected to increase mean levels of P_{PT} due to a resulting rise in flow rate through distal nephron segments, which have a

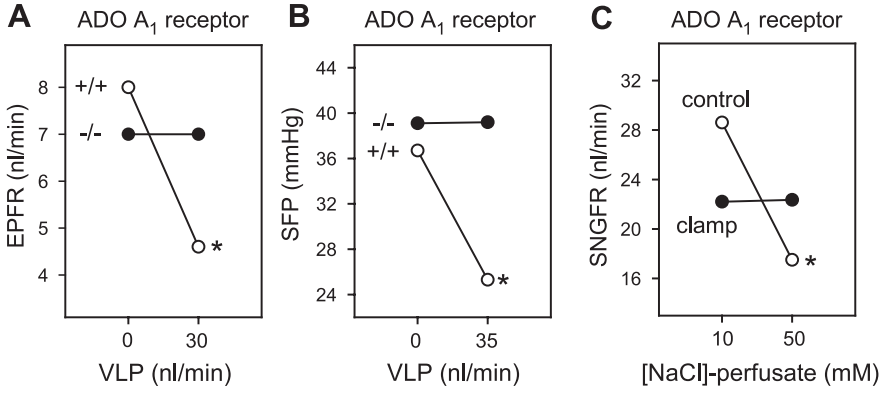

FIG. 6. Tubuloglomerular feedback responses in wild-type mice (+/+) and mice deficient (−/−) for adenosine (ADO) A_1 receptor (*A* and *B*), and in rats with clamping of ADO A_1 receptor activation (*C*). *A* and *B:* response in early proximal flow rate (EPFR) or proximal stop-flow pressure (SFP) to an increase in loop of Henle perfusion rate (VLP) is blunted in −/− mice. *$P < 0.05$ vs. 0 nl/min loop perfusion. [Adapted from Brown et al. (38) and Sun et al. (322).] *C:* clamping of ADO A_1 receptor activation (see text for procedure) blunted tubuloglomerular feedback (TGF) response assessed as the change in single-nephron GFR (SNGFR; by paired proximal collections) during retrograde perfusion of the macula densa segment from the early distal tubule with artificial tubular perfusate containing either 10 or 50 mM NaCl to induce minimum and maximum stimulation of TGF. *$P < 0.05$ vs. 10 mM. [Adapted from Thomson et al. (330).]

high flow resistance (194). The concomitant increase of the luminal NaCl concentration at the macula densa lowers SNGFR through the TGF mechanism and as a consequence should reduce the influence of flow alterations upon P_{PT}. It was reported that the initial rise in P_{PT} in response to adding 2–15 nl/min of artificial tubular fluid to the free-flowing proximal tubule was not different between wild-type mice and mice lacking adenosine A_1 receptors (348). Notably, the subsequent fall in P_{PT}, as determined in the second minute of adding fluid, was likewise similar between genotypes at flow rates of 2, 4, 6, and 10 nl/min, indicating that mechanisms independent of adenosine A_1 receptors and TGF can fully substitute to stabilize P_{PT}. These mechanisms may include an adaptation of tubular reabsorption and/or luminal diameter. In response to a supraphysiological flow rate of 15 nl/min, however, P_{PT} in the second minute remained at higher values in mice lacking adenosine A_1 receptors than in wild-type mice, indicating an overriding of compensating mechanisms. These data suggest that in the physiological flow range, adenosine A_1 receptor- and TGF-mediated control of SNGFR is not required for normal flow-dependence of P_{PT}. Long-term consequences of using primarily TGF-independent mechanisms to stabilize P_{PT}, however, may have disadvantages that remain to be discovered (348).

Activation of the TGF mechanism may contribute to the reduction of GFR caused by lowering proximal tubular reabsorption in response to carbonic anhydrase inhibitors, which are diuretics (264, 340). To test this concept, Hashimoto and colleagues (119) elucidated the effect of the carbonic anhydrase inhibitor benzolamide on renal hemodynamics in adenosine A_1 receptor knockout mice, which as outlined above lack a TGF response. It was observed, however, that the absence of a functional TGF mechanism did not prevent the reduction in GFR or renal blood flow caused by carbonic anhydrase inhibition. On the other hand, acute angiotensin II receptor blockade diminished the effect of carbonic anhydrase inhibition on GFR and renal blood flow in either genotype (119). The authors concluded that TGF activation is not necessary for the decline in GFR caused by carbonic anhydrase inhibitors and that the GFR reduction appears to be the consequence of a combination of an angiotensin II-dependent reduction in renal plasma flow and a diuresis-induced increase in P_{PT}.

To gain more insights on the functional consequences of a lack of adenosine A_1 receptors and TGF on the single-nephron level, distal SNGFR and Na^+ delivery were determined under free-flow conditions in response to adding 6 nl/min of artificial tubular fluid to the last surface loop of the proximal tubule. Consistent with TGF activation, this maneuver lowered distal SNGFR in wild-type mice, determined by distal tubular collection, i.e., downstream from the macula densa. In comparison, distal SNGFR remained basically unaltered in response to this maneuver in mice lacking adenosine A_1 receptors. Importantly, as a consequence of the blunted SNGFR response, the increases in distal tubular flow rate and Na^+ delivery were significantly greater in the absence of adenosine A_1 receptors. These experiments demonstrate the role of adenosine A_1 receptor- and TGF-mediated control of GFR in stabilizing the Na^+ delivery to the distal tubule (348).

A similar conclusion derived from studies in which aquaporin-1 knockout mice and adenosine A_1 receptor knockout mice were crossed to generate an animal model that combines a proximal tubular absorption defect with absence of TGF regulation of GFR. Aquaporin-1 knockout mice present reduced proximal reabsorption (295, 352) and, possibly as a consequence of the resulting TGF activation, a lower GFR than wild-type mice, which prevents fluid and NaCl loss through the kidney (295). Consistent with this assumption, deleting the adenosine A_1 receptor in aquaporin-1 knockout mice normalized GFR (118). As a consequence of normal GFR in the presence of reduced proximal reabsorption, however, distal fluid and Cl^- delivery were greatly enhanced in the double knockout mice. Nevertheless, these mice have normal renal NaCl excretion, normal arterial blood pressure, and only a small increase in plasma renin concentration. Thus, in the chronic setting, distal transport mechanisms can almost fully compensate for proximal tubule malabsorption in the absence of TGF-induced reduction of GFR (118). Whether shifting of significant portions of the transport load from the proximal to the distal nephron, however, affects the ability for fine regulation of salt balance and/or affects other aspects of kidney function and body homeostasis remains to be determined.

D. Adenosine Is a Mediator of TGF

The above findings demonstrate that adenosine and adenosine A_1 receptors are involved in macula densa control of GFR. The exact role of adenosine, however, was not addressed in the above experiments. Adenosine in the interstitium of the JGA could establish a relatively constant vasoconstrictor tone that provides a necessary background for another mediator to elicit the TGF response and thus adenosine may act as a *modulator* of TGF. Alternatively, intact TGF may require local adenosine concentrations in the JGA to fluctuate directly in dependence of the luminal NaCl concentrations at macula densa, which would implicate that adenosine is a *mediator* of TGF. To discriminate between these alternatives, the question was asked whether local adenosine A_1 receptor activation in the JGA must vary in dependence of the electrolyte concentration at the macula densa for a normal TGF response to occur. To address this issue, we performed micropuncture experiments in which local

adenosine A_1 receptor activation at the JGA was clamped by combining pharmacological inhibition of 5′-nucleotidase (and thus adenosine generation) by AMPCP with adding back constant amounts of the adenosine A_1 receptor agonist CHA (330). If local adenosine would just induce a relative constant adenosine A_1 receptor-mediated vasoconstrictor tone to establish a necessary background for another mediator to elicit the TGF response, then the above maneuver should not inhibit the TGF response. It was observed, however, that this maneuver significantly reduced the slope of the TGF curve in free-flow experiments. Moreover, clamping of adenosine A_1 receptor activation as described completely inhibited the fall in SNGFR in response to retrograde perfusion of the macula densa segment from early distal tubular site with low and then high NaCl concentrations in the perfusate (330) (see Fig. 6*C*). Thus TGF is attenuated by adenosine A_1 receptor blockade or inhibition of 5′-nucleotidase-mediated generation of adenosine and cannot be restored by establishing a constant adenosine A_1 receptor activation. These data suggest that local adenosine concentration must fluctuate for normal TGF to occur, indicating that adenosine is a mediator of TGF (330).

The concept proposed by Osswald et al. (251) that in the JGA adenosine couples energy metabolism with the control of GFR (and renin secretion), i.e., adenosine acts as a mediator of TGF, could be realized in the following manner (see Fig. 7): transport-dependent hydrolysis of ATP in macula densa cells (or in the cells of the TAL in close proximity to the JGA) would lead to enhanced generation of AMP. Involved ATPases include the basolateral Na^+-K^+-ATPase, which extrudes the Na^+ taken up across the apical membrane. In macula densa cells, the activity of this ATPase, however, may only be ~1/40 the activity of surrounding cells of cortical TAL (296). Thus, in contrast to the cells of TAL, much of the Na^+ may leave the macula densa cells via a $(Na^+)H^+$-K^+-ATPase that is expressed in the apical membrane (266, 354) (see Fig. 7). The AMP generated by these ATPases is dephosphorylated in the cell to adenosine by cytosolic 5′-nucleotidase or plasma membrane-bound endo-5′-nucleotidase, and the generated adenosine could be released through a nucleoside transporter into the interstitium of the extraglomerular mesangium. NaCl transport-dependent release of endogenous adenosine has been shown in the perfused shark rectal gland, a model epithelia for hormone-stimu-

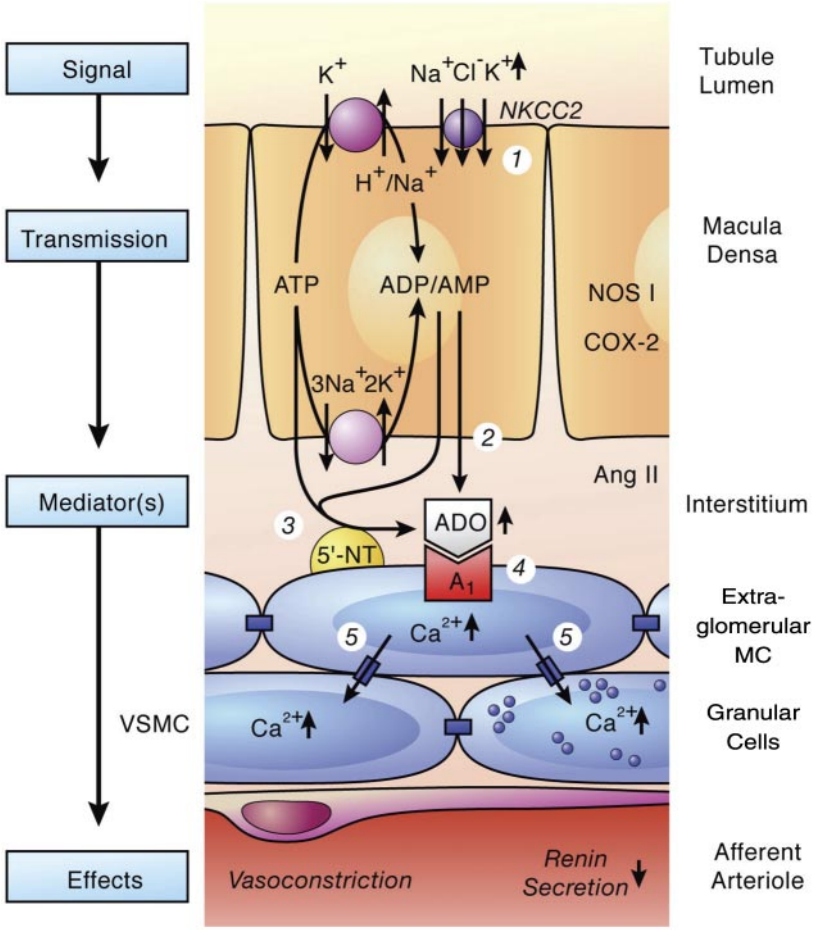

FIG. 7. Proposed mechanism of adenosine acting as a mediator of the tubuloglomerular feedback. Numbers in circles refer to the following sequence of events. *1*, Increase in concentration-dependent uptake of Na^+, K^+, and Cl^- via the furosemide-sensitive Na^+-K^+-$2Cl^-$ cotransporter (NKCC2); *2* and *3*, transport-dependent, intra- and/or extracellular generation of adenosine (ADO); the extracellular generation involves ecto-5′-nucleotidase (5′-NT); *4*, extracellular ADO activates adenosine A_1 receptors triggering an increase in cytosolic Ca^{2+} in extraglomerular mesangium cells (MC); *5*, the intensive coupling between extraglomerular MC, granular cells containing renin, and smooth muscle cells of the afferent arteriole (VSMC) by gap junctions allows propagation of the increased Ca^{2+} signal resulting in afferent arteriolar vasoconstriction and inhibition of renin release. Factors such as nitric oxide, arachidonic acid breakdown products, or angiotensin (ANG) II modulate the described cascade. NOS I, neuronal nitric oxide synthase; COX-2, cyclooxygenase-2. See text for further explanations. [Adapted from Vallon (342).]

lated electrolyte transport (159) as well as medullary TAL (19, 21) (see also sect. II). Alternatively or in addition, AMP may leave the macula densa cells and plasma membrane-bound ecto-5′-nucleotidase converts it to adenosine in the interstitium. The 5′-nucleotidase inhibitor AMPCP, which inhibited TGF in the above-mentioned micropuncture studies (330), is supposed to inhibit plasma membrane-bound 5′-nucleotidase but not AMP-specific cytosolic 5′-nucleotidase (380). Thus plasma membrane-bound ecto- or endo-5′-nucleotidase may serve to generate the adenosine mediating the TGF response. In this regard, two mouse models that lack ecto-5′-nucleotidase have more recently been shown to present attenuated TGF responses, indicating that this ecto-enzyme in fact contributes to the adenosine pool mediating the TGF response (45, 134). Huang et al. (134) showed that the remaining TGF activity of mice lacking ecto-5′-nucleotidase is abolished by the adenosine A_1 receptor blocker DPCPX. This indicated that ecto-5′-nucleotidase-dependent and -independent generation of adenosine participates in the mediation of TGF. The ecto-5′-nucleotidase independent fraction may reflect direct adenosine release from macula densa cells. Extracellular adenosine then binds to adenosine A_1 receptors at the surface of extraglomerular mesangial cells (242, 311, 337, 357) and increases cytosolic Ca^{2+} concentrations (242). Because of the intensive coupling by gap junctions between extraglomerular mesangial cells and granular cells as well as ordinary smooth muscle cells of glomerular arterioles, intracellular Ca^{2+} transients could be transmitted to these target structures inducing afferent arteriolar constriction (and inhibition of renin release) (139, 278).

Alternatively or in addition, the source of ATP being used for local adenosine formation may not directly contribute to macula densa transport; recent in vitro studies suggested that ATP itself could be released across the basolateral membrane of macula densa cells through a large-conductance anion channel in dependence of changes in the NaCl concentration in the luminal tubular fluid at the macula densa (23, 173). It was further proposed that the released ATP itself through activation of purinergic P2 receptors triggers an increase in cytosolic Ca^{2+} in the extraglomerular mesangium cells and/or the smooth muscle cells of the afferent arteriole, and thus ATP acts as the principal mediator of TGF (22, 239). Even though substantial evidence points to a role of ATP and P2X1 receptors in renal autoregulation (142, 239), no data have been published that indicate a direct role of a P2 receptor in the TGF response, such as studies with selective receptor antagonists or in knockout mice demonstrating inhibition of macula densa-dependent control of SNGFR. Moreover, Ren et al. (279) microperfused rabbit afferent arterioles and attached macula densas simultaneously in vitro and found that adding the P2 purinergic receptor inhibitor suramin to both arteriole lumen and bath did not significantly inhibit the TGF response. Considering on the other hand the outlined existing evidence for adenosine, ecto-5′-nucleotidase and adenosine A_1 receptors in mediating TGF, it seems possible that ATP being released from the macula densa is converted in the interstitium by ecto-ATPase and ecto-5′-nucleotidase to adenosine. Thus a model could be envisioned in which both ATP and adenosine would be considered mediators of TGF, since both are released or generated, respectively, in dependence of the NaCl concentration at the macula densa and both are part of a signaling cascade, in which adenosine via adenosine A_1 receptor activation triggers the final effects of the TGF response, i.e., preglomerular vasoconstriction. Further studies on the role of ecto-ATPase as well as P2-type purinergic receptors in the TGF response are required, including studies in knockout mice, to delineate the relationship between adenosine and ATP in TGF signaling.

E. Concluding Remarks

The available experimental evidence including studies in adenosine A_1 receptor knockout mice clearly indicates a role of adenosine and adenosine A_1 receptors in macula densa control of GFR. More recent experiments suggest that an intact TGF requires local concentrations of adenosine to fluctuate in dependence of the electrolyte concentration in the tubular fluid at the macula densa, indicating that adenosine is not just a *modulator* but actually serves as a *mediator* of TGF. Potential implications for a metabolic control of kidney function are outlined in section VIII.

VI. ADENOSINE AND RENIN RELEASE

The renin-angiotensin-aldosterone system plays a central role in electrolyte homeostasis and in the regulation of blood pressure. The level of activity of this system is determined primarily by the rate at which the kidneys secrete renin into the circulation. Major stimuli that control renal renin release include the renal perfusion pressure, sympathetic nerve activation, and the NaCl concentration sensed by the macula densa in the early distal tubule. Much has been learned in recent years on the signaling cascades involved in the control of renal renin secretion, indicating primary roles for prostanoids, NO, and angiotensin II in this process (for review, see Refs. 114, 262, 301). Here we outline the evidence for a role of adenosine in the regulation of renal renin secretion. This topic has previously been reviewed in 1990 by Churchill and Bidani (48) and by Jackson in 1991 (146) and 1997 (147).

A. Effects of Exogenous Adenosine Agonists on Renin Release

In 1970, Tagawa and Vander (325) reported that adenosine infusion into the renal artery of salt-depleted dogs leads to a sustained inhibition of renal renin secretion into the venous blood. This inhibitory effect of adenosine on renin release was subsequently confirmed in dogs (8, 59, 61, 207, 314) and rats (47, 254); in isolated perfused rat kidneys (230, 231), rat kidney slices (49–51, 285), isolated perfused glomeruli (309); in isolated renin secreting cells (3), short-term cultures of juxtaglomerular cells (179); and in humans (71). The adenosine-induced inhibition of renin release is mediated by adenosine A_1 receptors as specific agonists and antagonists for this receptor type can mimic or block the inhibitory actions of exogenous adenosine on renin secretion, respectively (for review, see Ref. 147). In contrast to adenosine A_1 receptor stimulation, activation of adenosine A_2 receptors can lead to an increase of renin secretion (47, 49). Whether this stimulatory effect of adenosine A_2 receptor activation is of physiological significance remains to be determined.

Adenosine can inhibit catecholamine release from sympathetic nerve endings in the kidney (120, 121). Because β-adrenergic receptor activation leads to an increase in renin release, it was argued that the inhibitory effect of adenosine on renin secretion might result from inhibition of catecholamine release. This issue was addressed in anesthetized rats with unilateral renal denervation. The studies showed that renal innervation is not required for effects of adenosine on renal renin secretion (52). In accordance, isolated superfused renin-containing cells from rat kidneys respond to adenosine with a reduced renin secretion rate (3). The latter studies also indicated that adenosine receptors are located on renin-containing cells. Further studies suggested that inhibition of renin secretion by adenosine A_1 receptor activation involves increases in intracellular Ca^{2+} that are pertussis toxin sensitive and thus could result from receptor-induced inhibition of adenylyl cyclase (285).

B. Role of Endogenous Adenosine in the Control of Renin Release

Evidence for an inhibitory action of endogenous adenosine on renin secretion was provided by experiments in which renal adenosine concentrations were elevated by administration of the adenosine reuptake inhibitor dipyridamole (11, 324) or by ATP depletion using maleic acid (10). Most notably, a single application of the adenosine A_1 receptor antagonist FK-453 was found to increase plasma renin concentrations in humans (15), indicating a tonic inhibition of renin secretion by adenosine A_1 receptor activation. Furthermore, the stimulation of renin secretion by various maneuvers [including a reduction in renal artery pressure (60, 178), low-Na^+ diet (177, 339), hydralazine (334), diazoxide (37), furosemide (259), and isoproterenol (267)] can be further increased by application of adenosine receptor antagonists. Under some of these conditions, the apparent NaCl concentration sensed at the macula densa and thus macula densa-dependent generation of adenosine should be rather low (e.g., reduced renal artery pressure or furosemide application, which also blocks the Na^+-$2Cl^-$-K^+ cotransporter in the macula densa). Therefore, the source of adenosine that suppresses renin secretion during these maneuvers may not primarily be regulated by the NaCl concentration in the luminal fluid at the macula densa. An increase in intracellular cAMP is an important stimulator of renin release from juxtaglomerular cells (89). Jackson and Raghvendra (149) suggested that increases in intracellular cAMP in renin-secreting cells cause efflux of cAMP, which activates the extracellular cAMP-adenosine pathway, i.e., cAMP is converted to adenosine in the extracellular space (see Fig. 2). The generated adenosine by acting on adenosine A_1 receptors on the renin-secreting cells then acts as a negative-feedback control on renin release (149). Consistent with the notion that the renin-secreting cells themselves can supply adenosine or its precursor is a recent study in freshly isolated juxtaglomerular cells showing that superfusion with the adenosine A_1 receptor antagonist DPCPX enhances renin secretory rates (3). Notably, Schweda et al. (302) recently demonstrated by either pharmacological blockade with DPCPX or genetic deletion (adenosine A_1 receptor deficient mice) that adenosine A_1 adenosine receptors are indispensable for the inhibition of renin secretion by an increase in blood pressure. The authors concluded that formation and action of adenosine is responsible for inhibition of renin release in response to an increase in renal perfusion pressure, which may include adenosine derived from renin-secreting cells and/or macula densa-dependent mechanism (302).

Intrarenal infusion of hypertonic saline, a maneuver that leads to a sustained vasoconstriction (93), a fall in ATP, and an increase in adenosine levels in the kidney (250, 251), also reduced renal renin secretion (93). Notably, the fall in GFR in response to hypernatremia or maleic acid involved TGF activation (190, 291), most likely due to resulting increases in macula densa NaCl concentrations. Moreover, the inhibition of renin secretion under these conditions can be blocked by adenosine receptor antagonists (43, 93, 94, 318). These findings indicated that adenosine receptor activation may contribute to the inhibition of renin release in response to high NaCl concentrations at the macula densa. More evidence was provided by studies in isolated perfused macula densa segments with glomerulus attached. Skott and Briggs and colleagues (310, 361) demonstrated in this preparation

that enhancement of NaCl concentrations in the tubular fluid passing the macula densa cells inhibits renin release (see Fig. 8). Most importantly, this inhibition was susceptible to antagonism of adenosine A_1 receptors. Moreover, adenosine A_1 receptor antagonism inhibited renin secretion only at high but not at low NaCl concentrations at the macula densa (204, 361) (see Fig. 8). Further evidence that renin-containing cells are under tonic inhibition by macula densa cells was indicated by studies in isolated afferent arterioles (144). As shown in these experiments, the presence of macula densa cells on isolated afferent arterioles resulted in a much lower renin secretory rate compared with afferent arterioles without macula densa attached. Furthermore, this inhibitory effect of macula densa cells could be blocked by the adenosine receptor antagonist theophylline, indicating a role for adenosine in this tonic inhibition (144). In comparison, theophylline did not alter renin secretion in afferent arterioles without macula densa attached. In the latter studies, the macula densa segment was not perfused and the luminal NaCl concentration sensed by the macula densa most likely resembled the high NaCl concentrations in the incubation medium (144). Thus this latter study as well as the abovementioned study in isolated perfused macula densa segments with glomerulus attached are consistent with the notion that high NaCl concentrations in the tubular lumen enhance adenosine generation in a macula densa-dependent way and the adenosine generated inhibits renin release via activation of adenosine A_1 receptors.

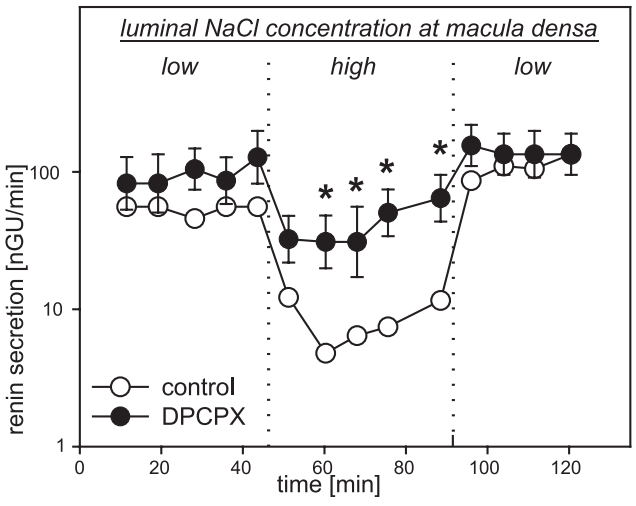

FIG. 8. Effect of the adenosine A_1 receptor antagonist DPCPX on changes in renin release provoked by altering the luminal NaCl concentration in the isolated macula densa-perfused and superfused juxtaglomerular apparatus (JGA) preparation in rabbits. In control experiments, a high NaCl concentration in the perfusate inhibited renin secretion. DPCPX, applied continuously to the bath, did not significantly alter renin secretion at low NaCl concentrations at the macula densa but blunted the effect of high NaCl ($*P < 0.05$ vs. control). [Adapted from Weihprecht et al. (361).]

Consistent with the role of adenosine A_1 receptors exerting a tonic suppression of renin synthesis and release are also two more recent studies in adenosine A_1 receptor knockout mice that revealed significantly increased renal mRNA expression and content of renin (303) as well as plasma renin activity in the knockout compared with wild-type mice (38). Moreover, the increases in renal mRNA expression and content of renin to dietary NaCl restriction were markedly enhanced in mice lacking adenosine A_1 receptors (303). This is consistent with the previously described further increase in renin release under low-NaCl diet by pharmacological blockade of adenosine receptors (177, 339). In comparison, the suppression in renal mRNA expression and content of renin in response to increasing dietary NaCl was not affected in adenosine A_1 receptor knockout mice. In additional experiments, furosemide, which inhibits the sensing of the TGF signal at the macula densa, led to similar increases in renal renin secretion in the isolated perfused kidney of adenosine A_1 receptor knockout and wild-type mice. From these two series of experiments the authors concluded that adenosine A_1 receptors do not play a role in the mediation of macula densa control of the renin system (303). This interpretation appears straightforward when the NaCl concentrations sensed by the macula densa go from normal to low, as assessed in the described furosemide experiments. Under these conditions, suppression of renin by cyclooxygenase-2-derived prostanoids plays a major role (114). Moreover, the tonic inhibition of renin release by adenosine A_1 receptor activation under these conditions may primarily be due to cAMP release from renin-secreting cells and extracellular conversion to adenosine inducing feedback inhibition of renin release as described above (149). The described experiments in adenosine A_1 receptor knockout mice, however, may not provide insights under conditions of high NaCl concentrations at the macula densa. This is because an increase in NaCl intake may not significantly alter the luminal TGF signal (but inhibit transport in the further distal aldosterone-sensitive segments) (345). A high-NaCl diet may have suppressed the renin system primarily independent of the macula densa system. Thus the concept that adenosine A_1 receptor activation contributes to the suppression of the renin system in response to high NaCl concentrations at the macula densa may not have been tested by a high-NaCl diet. In fact, Kim et al. (160) reported more recently that intravenous injection of NaCl (5% body wt), which increases the NaCl concentration at the macula densa and thus can assess the inhibitory part of the renin regulatory pathway (175), reduced plasma renin concentration to about half in conscious wild-type mice but did not induce significant changes in mice lacking adenosine A_1 receptors. These data support the concept, as strongly suggested by the studies outlined in the previous paragraph, that inhibition of renin secretion in

response to an increase in NaCl at the macula densa requires adenosine and activation of adenosine A_1 receptors (see Fig. 7).

C. Concluding Remarks

There is unequivocal evidence that adenosine A_1 receptor activation leads in vivo and in vitro to an inhibition of renin secretion. Obviously, adenosine A_1 receptors are not critical for the inhibition of renal renin release in response to an increase in dietary NaCl intake or for the increase in renin release in response to altering the NaCl concentrations sensed by the macula densa from normal to low. Studies employing acute blockade or chronic deficiency of adenosine A_1 receptors rather indicate a modulating, tonic inhibition of the renin system by adenosine. The source of adenosine that mediates this tonic inhibition may include the renin secreting cells, which release cAMP, and the cAMP-adenosine pathway acts as a negative-feedback control or brake of renin secretion. In addition, a macula densa-dependent source of adenosine and activation of adenosine A_1 receptors contribute to renin release inhibition under conditions of high NaCl concentrations at the macula densa.

VII. ROLE OF ADENOSINE IN FLUID AND ELECTROLYTE TRANSPORT IN THE KIDNEY

Adenosine can affect fluid and electrolyte transport in the kidney indirectly through effects on renal blood flow, GFR, and renin release. In this section the evidence for a direct effect of adenosine on fluid and NaCl transport in the tubular and collecting duct system is summarized. Table 2 provides an overview on the cellular second messenger systems linked to the adenosine receptors along the tubular and collecting duct system.

A. Proximal Tubule

In vitro studies in microperfused rabbit proximal tubule or cultured rat proximal tubular cells showed that endogenously formed adenosine stimulates proximal tubular reabsorption of fluid, Na^+, HCO_3^-, and phosphate by activation of adenosine A_1 receptors (41, 42, 326). The extracellular source of adenosine may include extracellular formation from cAMP by ecto-5′-nucleotidase in the brush-border membrane (which is sensitive to inhibition by nitric oxide) (306). Studies in a human proximal tubule epithelial cell line similarly revealed that adenosine A_1 receptor activation stimulates Na^+-dependent phosphate transport (328). In vivo studies in rats including both lithium clearance experiments as well as micropuncture experiments demonstrated that *1*) systemic application of a selective adenosine A_1 receptor antagonist (such as CVT-124, DPCPX, or KW-3902) elicits diuresis and natriuresis, and *2*) these responses are predominantly due to inhibition of reabsorption in the proximal tubule (169, 220, 367). The same conclusion was derived from studies in humans with application of the adenosine A_1 receptor antagonist FK-453 (15, 353). In comparison, no effects on absolute or fractional renal excretory function could be observed in response to the adenosine A_3 receptor antagonists MRS-1191 and MRS-1220 in the rat (227).

In general, natriuretics that act proximal to the aldosterone-sensitive distal nephron stimulate K^+ secretion in the latter segment and thus increase renal K^+ excretion. The finding that adenosine A_1 receptor antagonists do not increase renal K^+ excretion combined with the expression of adenosine A_1 receptors in the collecting duct (see Table 1) suggests that adenosine A_1 receptors may also affect K^+ secretion in the distal nephron. As a consequence, selective adenosine A_1 receptor antagonists are being developed as eukaliuretic natriuretics in Na^+-retaining states such as heart failure (97, 98, 363). Notably, basal proximal tubular reabsorption of fluid and Na^+ was not different in mice lacking adenosine A_1 receptors compared with littermate wild-type mice, indicating effective compensation (348).

Similar to selective adenosine A_1 receptor blockade, systemic application of the methylxanthines theophylline or caffeine is known to induce natriuretic and diuretic responses. Because methylxanthines are nonselective adenosine receptor antagonists (86), the observed changes in urine excretion may result from inhibiting the renal actions of endogenous adenosine. In fact, experiments in knockout mice demonstrated that intact adenosine A_1 receptors are necessary for both caffeine- and theophylline-induced inhibition of renal Na^+ and fluid reabsorption. These findings strongly suggest that adenosine A_1 receptor blockade mediates the natriuresis and diuresis in response to these methylxanthines (281).

The intracellular signaling pathways that contribute to adenosine A_1 receptor-mediated increases in proximal tubular reabsorption are still under investigation but may include increases of intracellular Ca^{2+} (68) and/or reductions of intracellular cAMP levels (174). Notably, studies in opossum kidney cells indicated that activation of adenosine A_1 receptors exerts a bimodal effect on the Na^+-H^+ exchanger NHE3, which is known to play a major role for Na^+ reabsorption in proximal tubule (349): low concentrations ($<10^{-8}$ M) of the adenosine analog N^6-cyclopentyladenosine (CPA) stimulated NHE3 and high concentrations ($>10^{-8}$ M) inactivated NHE3. Moreover, CPA-induced control of NHE3 was blocked by adenosine A_1 receptor antagonists (68). The inactivation of NHE3 by adenosine was suggested to involve calcineurin homologous protein-mediated regulation of NHE3 (67). Whether

adenosine also exerts a biphasic effect on proximal tubular reabsorption in vivo, as it was shown for angiotensin II (113), remains to be examined. Nevertheless, a biphasic effect of adenosine via adenosine A_1 receptors on proximal reabsorption could explain the observations that both adenosine A_1 receptor antagonists (inhibiting the effect of low endogenous adenosine concentrations, see above) as well as intrarenal delivery of adenosine A_1 receptor agonists (372) can induce natriuresis. In summary, basal proximal tubular reabsorption depends in part on tonic activation of adenosine A_1 receptors.

B. Medullary Thick Ascending Limb

In contrast to the proximal tubule, adenosine via activation of adenosine A_1 receptors appears to primarily inhibit NaCl reabsorption in medullary TAL. In vitro studies in cultured cells derived from rabbit or rat medullary TAL show that adenosine by activation of adenosine A_1 receptors can increase intracellular Ca^{2+} and inhibits vasopressin-induced activation of adenylyl cyclase and thus can potentially interfere with renal concentrating mechanisms (40, 335). Further evidence for adenosine A_1 receptor-mediated inhibition of transport was provided by experiments in isolated perfused medullary TAL of rat kidney. These studies demonstrated that application of adenosine (10^{-9} M) by activating adenosine A_1 receptors inhibits the net flux of chloride by 50% (20). It was further shown in isolated rat medullary TAL that this nephron segment is a site of adenosine release and that adenosine release in this segment is enhanced significantly during hypoxic conditions (21). This is relevant since the renal medulla is known to have a low partial oxygen pressure (36). The increased release of adenosine during hypoxia in medullary TAL was prevented by inhibitors of ion transport (21). In accordance, forcing transport in isolated mouse medullary TAL by application of hypertonic NaCl solution enhanced adenosine release (19). Consistent with a tonic activation of Na^+ reabsorption by adenosine A_1 receptor activation in the medulla and thus potentially in medullary TAL are the findings that infusion of the adenosine A_1 receptor antagonist DPCPX into the renal medulla did not change medullary blood flow but increased Na^+ excretion (381). Micropuncture experiments in knockout mice provided further evidence for a tonic, adenosine A_1 receptor-mediated inhibition of Na^+ reabsorption in a water-impermeable segment of the loop of Henle, possibly the TAL (348). On the other hand, there is evidence in rat TAL that activation of adenosine A_{2a} receptors can stimulate apical 70-pS K^+ channel activity via a PKA-dependent pathway (195), but the physiological relevance of these findings remains to be determined. In summary, the available evidence supports the concept that *1*) adenosine is released into the renal medulla by medullary TALs in dependence of transport activity and oxygen supply, and *2*) the released adenosine via activation of adenosine A_1 receptors inhibits NaCl absorption in the same nephron segments.

C. Distal Convoluted Tubule and Cortical Collecting Duct

Studies in a mouse distal convoluted tubule cell line revealed that adenosine has dual effects on Mg^{2+} uptake in these cells, namely, stimulation or inhibition via activation of adenosine A_1 or A_2 receptors, respectively (152). Experiments in cultured rabbit cortical collecting duct (CCD) cells revealed that adenosine interacts with an apical adenosine A_1 receptor to stimulate Ca^{2+} transport via a hitherto unknown pathway that does not involve cAMP formation, PKC activation, and/or Ca^{2+} mobilization (128). This stimulation of Ca^{2+} transport was confirmed in immunodissected rabbit connecting tubules and CCD cultured to confluence, and a role for a phorbol ester-insensitive PKC isoform was proposed in this response (130). Mg^{2+} and Ca^{2+} transport across the apical membrane in these segments is mediated by members of the transient receptor potential cation channel family, namely, TRPM6 (46) and TRPV5 (129), respectively. Thus these findings provide evidence for a role of adenosine in the regulation of these channels. With the use of the patch-clamp technique, it was further shown in a cell line derived from rabbit CCD that adenosine by binding to adenosine A_1 receptors and subsequent G protein-dependent activation of PLC and protein kinase C activates a Cl^- channel in the apical membrane (304). This Cl^- channel is known to contribute to the regulatory volume decrease in response to cell swelling. Moreover, studies in an immortalized cell line derived from rabbit distal bright convoluted tubule showed that swelling- and adenosine-activated Cl^- conductances share identical characteristics (287). Thus adenosine release during (ischemic) cell swelling may activate this Cl^- channel to restore cell volume.

D. Inner Medullary Collecting Duct

In primary cell culture of rat inner medullary collecting duct (IMCD) epithelium, agonists of adenosine A_1 receptors were found to inhibit the ability of vasopressin to stimulate the formation of cAMP (371), which is important for protein kinase A-dependent activation of the water channel aquaporin-2 in the apical membrane. It was further observed in these cells that adenosine inhibits epithelial water permeability (at 10^{-8} to 10^{-7} M) and apical Na^+ uptake (at 10^{-7} M to 1 μM) (370). Studies employing monolayers of a mouse IMCD cell line mounted in Ussing-type chambers demonstrated that

adenosine, which is released by a nucleoside transporter or is formed extracellularly by the breakdown of AMP, decreases vasopressin-stimulated electrogenic Cl^- secretion (IscCl) through activation of adenosine A_1 receptors (226). Moreover, Jackson et al. (148) showed that both freshly isolated collecting ducts and collecting duct cells in culture converted exogenous cAMP to AMP and adenosine. In both preparations, conversion of cAMP to AMP and adenosine was affected by a broad-spectrum phosphodiesterase inhibitor and a blocker of ecto-5′-nucleotidase in a manner consistent with exogenous cAMP being extracellularly processed to adenosine. Furthermore, in collecting duct cells in culture, stimulation of adenylyl cyclase increased extracellular concentrations of cAMP, AMP, and adenosine, and these changes were also modulated by the aforementioned inhibitors in a manner consistent with the extracellular cAMP-adenosine pathway (148). Thus the extracellular cAMP-adenosine pathway may be an important source of extracellular adenosine that may serve to feedback inhibit vasopressin-induced cAMP-mediated stimulation of Na^+ and fluid reabsorption in the IMCD.

E. Concluding Remarks

The in vitro and in vivo studies on kidney fluid and electrolyte transport indicate that under physiological conditions endogenous adenosine by activation of adenosine A_1 receptors stimulates NaCl reabsorption in cortical proximal tubule, which is a tubular segment with relatively high basal oxygen supply. In contrast, adenosine inhibits NaCl reabsorption in medullary TAL and IMCD, i.e., nephron segments with relatively low oxygen delivery. These direct and differential effects of adenosine on fluid and NaCl reabsorption are discussed with regard to a role of adenosine in metabolic control of kidney function in the next section.

VIII. ADENOSINE AND METABOLIC CONTROL OF ORGAN FUNCTION: DOES IT APPLY TO THE KIDNEY?

In this section we discuss the role of adenosine in the general concept of a metabolic control of kidney function, i.e., the regulation of the interrelation between energy supply and energy-consuming processes (see also Fig. 1). In other organs, adenosine is known to contribute to the metabolic control of organ function, and thus we analyze the various renal actions of adenosine on kidney function in this regard to assess whether also in the kidney adenosine actions contribute to the interrelation between energy supply and demand. If adenosine contributes to a metabolic control of kidney function, then we expect it will do so together with a variety of other factors and autacoids that similarly affect renal hemodynamics and/or renal transport processes.

In organs such as heart, skeletal muscle, or brain, blood flow is nutritive. Therefore, metabolic control of organ function requires a vasodilator to be released during enhanced organ work. Organ work enhances the formation of adenosine, which increases oxygen supply by causing vasodilation and increases blood flow in the heart, skeletal muscle, brain, and other tissues (25, 26, 33, 271, 299). Adenosine thus can contribute to maintain tissue oxygenation. In contrast to these organs, blood flow in the kidney cortex via GFR determines the transport work of the kidney. As outlined in Figure 9, the product of GFR and plasma Na^+ concentration determines the Na^+ load to the tubular system (F_{Na}). This Na^+ load on the other hand determines the Na^+ transport by the tubular and collecting duct epithelium (T_{Na}). This relationship is termed as the glomerular-tubular balance (GTB), which predicts that a relative constant fraction of the filtered load is reabsorbed by the tubular and collecting duct system. Under normal conditions, the system reabsorbs more than 99% of the filtered amount of fluid and NaCl and thus GFR determines T_{Na}. The main driving force for transcellular solute and water reabsorption in the kidney is the basolateral Na^+-K^+-ATPase. The activity of this enzyme is responsible for the major fraction of renal ATP hydrolysis and therefore for renal oxygen and substrate consumption. As a consequence, GFR determines to a great extent renal oxygen and substrate consumption and requirements (see Fig. 9, *parts 1–3*). In other words, in contrast to organs like heart, skeletal muscle, or brain, a metabolic control of kidney function could involve a vasoconstrictor that acts in kidney cortex to lower GFR and thus tubular work load.

As outlined in section II and depicted in Figure 9, *part 4*, in the last 20 years the available evidence clearly supports the assumption that also in the kidney adenosine is formed at an enhanced rate and extracellular adenosine concentrations increase when transport work increases and/or ATP tissue levels fall. Moreover, as outlined in sections IV and V, adenosine induces a sustained vasoconstriction of the afferent arterioles, especially in the outer cortex, and lowers GFR (see Fig. 9, *part 5*). The inverse relation between interstitial adenosine concentrations and GFR closes the negative-feedback loop depicted in Figure 9. The general principle of metabolic control of kidney function should include a cortical vasoconstrictor to lower GFR, and, as in other organs, adenosine may contribute to this control.

Two sites have to be considered for the inverse relationship between adenosine and GFR, namely, the JGA and the renal cortical interstitial space outside the JGA. Under physiological conditions, the site most important for the described inverse relationship between adenosine formation and GFR may be the JGA, i.e., the site of TGF

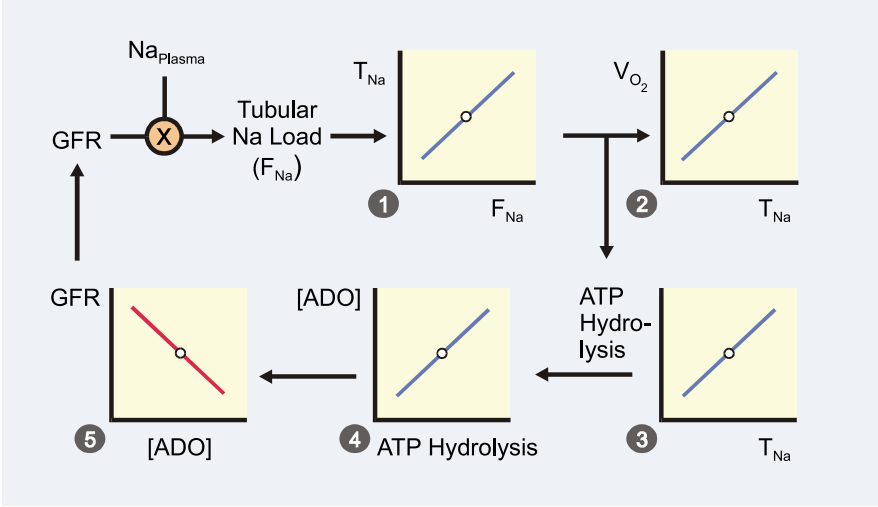

FIG. 9. Metabolic control of kidney function I. The line plots illustrate the relationships between the given parameters. Small circles on these lines indicate ambient physiological conditions. In the kidney, glomerular filtration rate (GFR) and the plasma concentration of Na^+ determine the Na^+ load to the tubular system (F_{Na}). Tubular Na^+ reabsorption or transport work (T_{Na}) is load-dependent (*1*) and determines renal oxygen consumption (Vo_2) (*2*) and ATP hydrolysis (*3*). Thus GFR is a determinant of renal transport work. It follows that in contrast to other organs, a vasoconstrictive metabolite that lowers GFR and thus transport work can contribute to a metabolic control in the kidney. Adenosine, which is formed by transport- and thus GFR-dependent ATP hydrolysis (*4*) or extracellular breakdown of ATP (data not shown), causes afferent arteriolar vasoconstriction and lowers GFR (*5*), and thus induces a negative feedback on tubular Na^+ load and transport work. [Adapted from Spielman and Thompson (321).]

(see Fig. 10, *parts 1–4*). The TGF establishes an inverse relationship between the Na^+, Cl^-, and K^+ concentration in the tubular fluid passing the macula densa and GFR. As outlined in section V, adenosine mediates the TGF. In the absence of primary changes in tubular transport, the TGF stabilizes GFR and thus also the tubular work load and renal O_2 consumption in the kidney from minute to minute. Under physiological conditions, autacoids having a short half-life and being generated at sites distant to the JGA are unlikely to affect the signal transduction within the JGA. For instance, generation of adenosine in the medulla is unlikely to affect directly the afferent arterioles of the juxtamedullary glomeruli. If, however, a global ischemia leads under pathophysiological conditions to a significant fall in ATP and a corresponding increase in adenosine in the renal interstitial space, then the preglomerular resistance vessels outside the JGA will be exposed to higher concentrations of adenosine, which can reduce GFR and thus ATP-consuming tubular work (see sect. IX).

Under physiological conditions, the adenosine generated in renal structures outside of the JGA may primarily be involved in local feedback loops to affect tubular transport and medullary blood flow rather than GFR. According to the GTB, an increase in the filtered amounts of Na^+ causes a near-proportional increase of Na^+ transport along the nephron, which at the sites of transport activity and ATP hydrolysis increases the adenosine concentrations in the extracellular space (see Fig. 10, *parts 5* and *6*). As described in section VII, in the cortical proximal tubule the ambient low extracellular concentrations of adenosine (~10–100 nM) stimulate the transport rate of Na^+ (see Fig. 10, *part 7*). A tonic, adenosine-mediated stimulation of cortical proximal tubular reabsorption reduces the work load delivered to the medullary parts of the proximal tubule and the loop of Henle, which pass through a kidney region in which blood flow and oxygen supply is much lower than in the cortex. In this regard, stimulation of proximal reabsorption by adenosine does not contradict the concept of metabolic control. We speculate that maintaining high rates of proximal reabsorption in the cortex is important to limit the transport load to downstream medullary segments that have limited substrate/oxygen supply. If this is important, then different independent systems may contribute to this regulation. To speculate further, the findings that acute pharmacological blockade but not chronic knockout of the adenosine A_1 receptor results in reduced proximal reabsorption may be due to activation of an adenosine-independent compensating system in the latter case that increases proximal reabsorption (see sect. VII). On the other hand, pathophysiological increases in adenosine as observed under conditions of oxygen deficiency may reduce reabsorption also in proximal tubule, and thus the response in proximal tubular reabsorption to adenosine is expected to be biphasic as outlined in section VII (see Fig. 10, *part 7*).

In contrast to the proximal tubule, in the medullary TAL and in the inner medullary collecting duct, i.e., nephron segments in a kidney region with low oxygen pressure and blood flow, adenosine is released or extracellularly formed in a transport-dependent fashion and decreases transport work (see sect. VII and Fig. 10, *part 8*). Especially the inhibition of reabsorption in the medullary TAL is expected to increase medullary partial O_2 pressures (36).

When the Na^+ transport capacity in the proximal tubule and/or TAL is saturated or inhibited, the TGF signal at the macula densa segment increases. This is followed by a TGF-induced, adenosine-mediated decline in SNGFR. This reduces the work load in the proximal tubule and the loop of Henle. Under pathophysiological conditions that significantly reduce the oxygen supply or induce an overwhelming oxygen demand in the proximal tubule or TAL, the adenosine-induced fall in GFR may

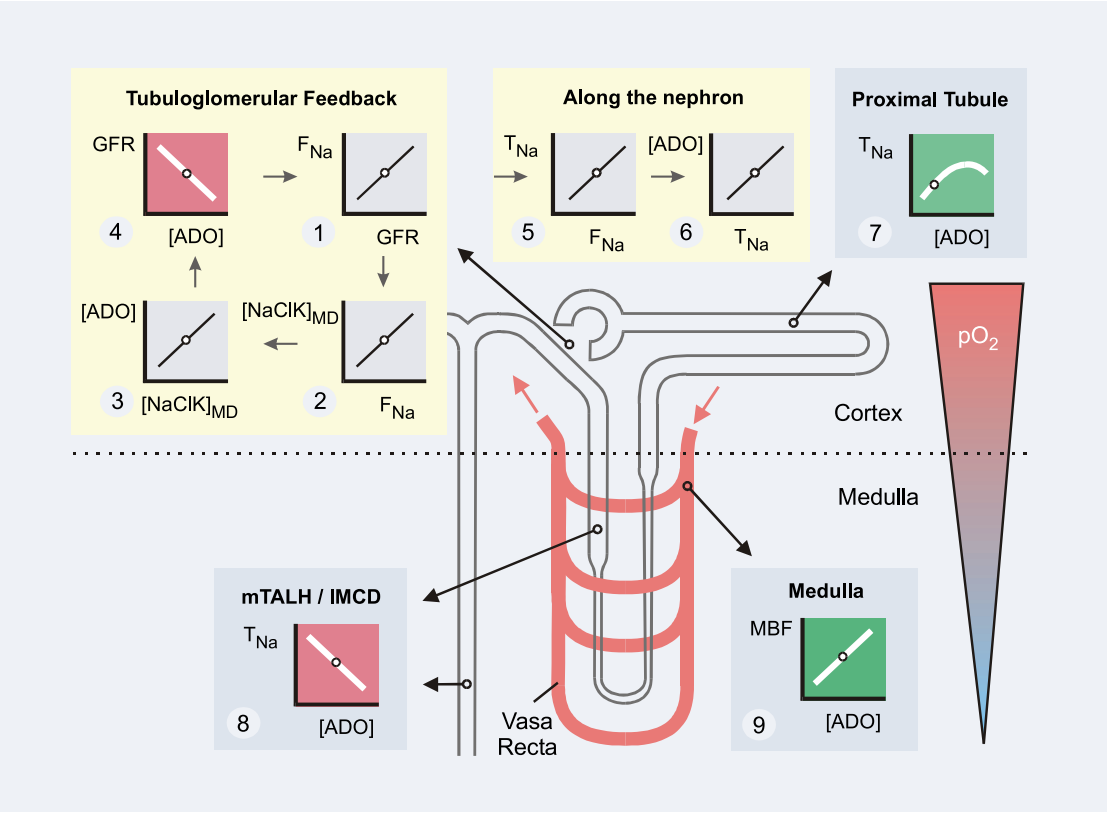

FIG. 10. Metabolic control of kidney function II. Partial oxygen pressure (pO_2) is lower in renal medulla than cortex, exposing the medulla to a greater risk for hypoxic damage. A concept is proposed that integrates the actions of extracellular adenosine (ADO) in the different regions of the kidney with respect to a protection of the medulla from hypoxic damage. The line plots illustrate the relationships between the given parameters. Small circles on these lines indicate ambient physiological conditions. *1*, A rise in GFR increases the Na^+ load (F_{Na}) to the tubular system in cortex and medulla. This increases the salt concentration sensed by the macula densa ($[Na\text{-}Cl\text{-}K]_{MD}$)(*2*), which enhances local ADO (*3*). *4*, ADO lowers GFR and thus F_{Na}, which closes a negative-feedback circle providing a basis for an oscillating system. *5*, F_{Na} determines Na^+ transport work (T_{Na}) and O_2 consumption in every nephron segment, and thus oscillations in F_{Na} may help protect the medulla. *6*, A rise in T_{Na} increases ADO along the nephron. *7*, In the cortical proximal tubule, ADO stimulates T_{Na} and thus lowers the Na^+ load to segments residing in the medulla. *8*, In contrast, ADO inhibits transport work in the medulla including medullary thick ascending limb (mTAL) and inner medullary collecting duct (IMCD). *9*, In addition, ADO enhances medullary blood flow (MBF), which increases O_2 delivery and further limits O_2 consuming transport in the medulla.

persist (see sect. IX). Under physiological conditions, however, the described mechanisms may actually induce oscillations. As described in section V, the TGF mechanism induces rhythmic oscillations of SNGFR, proximal tubular pressure, and distal NaCl delivery. Schurek and Johns (300) suggested that a limited oxygen supply to the nephron forces medullary TAL segments to oscillate between aerobic and anaerobic energy production. During the phase of a rising SNGFR, the transport load at one point overwhelms the capacity of medullary TAL for aerobic energy production. The resulting switch to anaerobic glycolysis reduces medullary TAL's transport efficiency dramatically. This increases the luminal TGF signal and initiates the declining phase of SNGFR. The reduced transport load reactivates aerobic energy production and efficient transport in medullary TAL and lowers the luminal TGF signal again. This initiates SNGFR to rise and closes the circle (see Fig. 10, *parts 1–4*). In addition to a potential role in NaCl balance (see sect. V), the oscillations in the tubular NaCl load and thus NaCl transport in medullary TAL may help to preserve the integrity of the renal medulla. As outlined in section V, mice deficient for the adenosine A_1 receptor lack these oscillations (348), and as outlined in section IX, ischemia-reperfusion-induced widespread tubular epithelial necrosis and vascular congestion in the outer medulla are enhanced by the absence or pharmacological blockade of adenosine A_1 receptors (188).

The kidney is a heterogeneous organ with different blood and oxygen supply to the cortex and medulla. As outlined, the high blood flow in the cortex initiates glomerular filtration and thus renal transport work. In comparison, medullary blood flow is low, to preserve osmotic gradients and enhance urinary concentration. As a consequence, O_2 delivery to the renal medulla is low. This is reflected by partial pressures of O_2 in the medulla in the range of 10–20 versus 50 mmHg in the cortex (36). Medullary hypoxia results both from countercurrent exchange

of O_2 within the vasa recta and from the consumption of O_2 by active transport in the medullary TALs. Renal medullary hypoxia is an obligatory part of the process of urinary concentration. When O_2 supply is further impaired, however, medullary hypoxic injury can develop. This is illustrated by the renal response to ischemia-reperfusion, which reveals widespread tubular epithelial necrosis and vascular congestion in the outer medulla (36, 241). Various intrarenal mechanisms act in concert to minimize medullary hypoxia (36). Adenosine-mediated actions like TGF-induced reductions or oscillations of the NaCl load to the tubular system, maintaining high proximal reabsorption, or inhibiting reabsorption in the medullary TAL can be part of these mechanisms (see above). As outlined in section IV and depicted in Figure 10 (*part 9*), adenosine being generated in the deep cortical and medullary region increases via adenosine A_2 receptor activation deep cortical and medullary blood flow and thus O_2 supply to the medulla. Furthermore, by washing out the high osmolality in the medullary interstitium, the adenosine A_2 receptor-mediated rise in medullary blood flow lowers medullary transport activity (381). Thus the actions of adenosine can contribute to stabilize the O_2 demand-to-supply ratio in this region of the kidney that is sensitive to hypoxic injury. In accordance, interstitial infusion of adenosine in rat kidney decreased partial pressure of O_2 in cortex but increased it in the medulla, consistent with an important regulatory and protective role of adenosine in renal medullary O_2 balance (66). Finally, ischemia-reperfusion-induced widespread tubular epithelial necrosis and vascular congestion in the outer medulla are significantly reduced by activation of adenosine A_1 or A_{2A} receptors (188, 241) but enhanced by the absence or pharmacological blockade of adenosine A_1 receptors (188)(see sect. IX).

In summary, whereas many other factors are likely to also contribute, a concept is proposed based on the differential renal actions of adenosine that this autacoid plays a vital role in the metabolic control of kidney function. Clearly, further experiments are required to validate this concept.

IX. PATHOPHYSIOLOGICAL ASPECTS

Various mechanisms and factors contribute to the pathophysiology of acute renal failure (ARF) (for review, see Ref. 35). The renal actions of adenosine would fit into some of the concepts of ARF in as much as adenosine is an intrarenal metabolite that can lower GFR and adenosine accumulates in the kidney during renal ischemia (see sect. II). Moreover, experimental models of ARF can be associated with increased expression of adenosine A_1 receptors in glomeruli, which may contribute to depressed GFR (312). Therefore, inhibition of adenosine vasoconstrictor actions in the kidney could be beneficial in conditions of ARF. On the other hand, the ARF-associated reduction in GFR and in tubular NaCl load may protect to some extent the tubular system from hypoxic injury, e.g., in ischemia-reperfusion. Moreover, and as outlined in section VIII, adenosine may protect the kidney and especially the renal medulla from hypoxic injury. Therefore, inhibition of adenosine receptors in ARF could be a two-sided sword. In the following we outline studies on the role of adenosine in ARF induced by radiocontrast media and ischemia-reperfusion, respectively.

A. Radiocontrast Media-Induced Acute Renal Failure

Application of radiocontrast media to humans can lead to an impairment of renal function including a fall in GFR. Even small changes in renal function have been associated with increased morbidity and mortality, making the prevention of radiocontrast nephropathy of paramount importance (362). When risk factors like volume and NaCl depletion are present, the severity of this impairment can result in ARF, and proven preventive measures include volume expansion with intravenous saline or sodium bicarbonate (362). Notably, unselective or adenosine A_1 receptor-selective antagonists can prevent renal impairment induced by radiocontrast media. This has been shown in dogs (5), rats (76), mice (186), and, most importantly, humans (75, 136, 137, 153, 154, 172). Moreover, wild-type mice developed significantly worse acute renal failure and more renal cortex vacuolization and had lower survival 24 h after radiocontrast media treatment compared with mice lacking the adenosine A_1 receptor (186). In contrast, application of dipyridamole, which increases extracellular adenosine concentrations, augmented the severity of renal impairment in response to radiocontrast media in dogs (5) and humans (154). Two studies indicated that the unselective adenosine receptor antagonist theophylline is as effective as saline hydration to prevent ARF in response to contrast media, but the benefits of the two maneuvers are not additive (1, 74). Thus use of theophylline can be beneficial in patients where sufficient hydration may be impossible or in patients with a concomitant decrease in renal blood flow (e.g., congestive heart failure or chronic renal insufficiency) (74, 136). A recent meta-analysis of clinical trials concluded that theophylline may reduce the incidence of radiocontrast media-induced nephropathy and recommended a large, well-designed trial to more adequately assess the role of theophylline in this condition. The authors also acknowledged the larger benefit of theophylline for studies with no predefined hydration protocol (13). Notably and as summarized in Table 4, unselective or A_1-selective adenosine receptor antagonists can pre-

TABLE 4. *Improvement of renal function by adenosine receptor antagonists in various models of nephrotoxic acute renal failure*

Models of ARF	Species	Adenosine Antagonist	Reference Nos.
Glycerol injection	Rat	Theophylline	29,30
		8-Phenyl-theophylline	34,377
		DPCPX	158,258
		FR-113453	143
		KW-3902	323
Uranylnitrate	Rat	Theophylline	248
Cisplatin	Rat	Theophylline	123
		DPCPX	170
		KW-3902	232
	Human	Theophylline	24
Contrast media	Dog	Theophylline	5
	Human	Theophylline	75,136,137,153,154,172
	Rat	DPCPX, KW-3902	76,374
Endotoxin	Rat	DPCPX	168
Amphotericin B	Rat	Theophylline	122
	Dog	Theophylline	95
Gentamicin	Rat	KW-3902	375

DPCPX, FR-113453, and KW-3902 are adenosine A_1 receptor selective antagonists. ARF, acute renal failure.

vent renal impairment also in response to other nephrotoxic substances.

B. Ischemia-Reperfusion Injury

Ischemia-reperfusion injury plays a major role in delayed graft function and long-term changes after kidney transplantation. It has become evident that the cellular and molecular mechanisms during ischemia and reperfusion resemble an acute inflammatory response (102). To what extent the acute cellular alterations persist and affect organ function at later time points remain unclear. Different animal studies assessed the effect of a single application of the unselective adenosine receptor antagonist theophylline on kidney function in ischemia-reperfusion studies. Animals were pretreated with theophylline or it was given at *day 5* after the renal ischemic/hypoxemic event as outlined in the following. Pretreatment with a single dose of theophylline in rats attenuated the reduction in renal blood flow and GFR observed during the initiation phase of postischemic ARF as determined ~1 h after releasing a 30- or 45-min occlusion of the renal artery (197). Similar results with theophylline were obtained in the rabbit (100). Notably, in rats subjected to a 60-min occlusion of the left renal artery, theophylline, given intravenously 20 min before the release of the renal artery clamp in doses that antagonize renal adenosine actions in vivo, improved the recovery of renal function after ischemic injury by increasing urinary flow rate, GFR (measured by inulin clearance), and histology assessed by morphometric quantification of tubular damage, tubular obstruction, and pathological alteration of glomeruli at 3 h after initiating reperfusion (126, 248). Similarly, single-dose pretreatment of rats with theophylline during a 30-min renal artery occlusion led to increased renal blood flow and GFR during the maintenance phase of ARF after 5 days, indicating that effects of theophylline in the acute phase affected the outcome in the maintenance phase. Furthermore, acute theophylline treatment given at 5 days after ischemia acutely increases renal blood flow and GFR in previously untreated rats, indicating that adenosine contributes to the suppression of renal blood flow and GFR in the maintenance phase of ischemic reperfusion injury (199). With regard to studies in humans, a single dose of theophylline, given early after birth, has beneficial effects in reducing the renal involvement and fall in GFR in asphyxiated full-term infants as determined over the first 5 days (14). In contrast, pretreating rats before renal artery occlusion for 30 min with dipyridamole, which increases extracellular adenosine concentrations, intensified the fall in renal blood flow and GFR determined ~1 h after releasing the clamp, and this impairment was blocked by theophylline (198). In summary, these data suggest that pretreatment with theophylline can exert beneficial effects in the initiation and maintenance phase of ischemia-reperfusion injury.

On the other hand, systemic intravenous infusion of adenosine (1.75 mg · kg^{-1} · min^{-1} iv × 10 min) 2 min before a 45-min ischemic insult was likewise reported to protect renal function against ischemia and reperfusion injury as indicated by lower blood urea nitrogen and creatinine and improved renal morphology after 24 h of reperfusion. The effects of adenosine were proposed to be mediated by adenosine A_1 receptors (182), involve G(i/o) proteins and PKC activation (183), and include a reduction in inflammation, necrosis, and apoptosis (185). In accordance, mice lacking adenosine A_1 receptors exhibited significantly higher plasma creatinines and worsened renal histology compared with wild-type mice at 24 h after subjecting the kidneys to 30 min of ischemia (188). Similarly, wild-type mice pretreated with an adenosine A_1 receptor antagonist or agonist demonstrated significantly worsened or improved renal function, respectively, after ischemia and reperfusion injury that was associated with increased or reduced markers of renal inflammation, respectively (188).

Further supporting the notion of beneficial effects of adenosine, continuous application in the reperfusion period of DWH-146e, a selective adenosine A_{2A} receptor agonist, protected kidneys from ischemia-reperfusion injury as evidenced by a lower rise in serum creatinine and blood urea nitrogen after 24 and 48 h of reperfusion. Histological examination revealed widespread tubular epithelial necrosis and vascular congestion in the outer medulla of vehicle-treated rats. These lesions were significantly reduced in DWH-146e-treated animals (241). Similarly, systemic adenosine given after 45 min of renal

ischemia but before reperfusion protected renal function, as indicated by lower rises in creatinine and less histologically evident renal tubular damage. Pharmacological maneuvers indicated that these effects of adenosine were mediated by adenosine A_{2a} receptor activation (184). Further studies suggested that protection from renal ischemia-reperfusion injury by adenosine A_2 receptor agonists or endogenous adenosine requires activation of adenosine A_2 receptors expressed on bone marrow-derived cells (57).

Finally, it was shown in rats that adenosine A_3 receptor stimulation deteriorated renal ischemia-reperfusion injury, whereas inhibition of adenosine A_3 receptors protected renal function as efficiently as preconditioning (182). In accordance, mice lacking the adenosine A_3 receptor presented significant renal protection, functionally and morphologically, from ischemic or myoglobinuric renal failure (187). The mechanisms of these A_3 receptor-mediated effects are not understood at present. One possibility is that the absence of adenosine A_3 receptors may be antiapoptotic because A_3 receptor activation has been shown to promote apoptosis in several cell lines including renal cells.

In summary, beneficial effects on GFR and renal morphology beyond 3–24 h of reperfusion after ischemia can be induced by *1*) pretreatment or treatment immediately before reperfusion with adenosine, *2*) pretreatment with adenosine A_1 receptor agonists, *3*) treatment immediately before or during reperfusion with adenosine A_{2a} receptor agonists, *4*) pretreatment with the unselective adenosine receptor antagonist theophylline, and *5*) deficiency of adenosine A_3 receptors. In comparison, the outcome is worsened by *1*) pretreatment with adenosine A_1 receptor antagonists or deficiency of adenosine A_1 receptors and *2*) pretreatment with adenosine A_3 receptor agonists. Because theophylline can inhibit both adenosine A_1 and A_{2a} receptors, and possibly acts as an agonist at adenosine A_3 receptors (77), the findings appear contradictory. Considering the clinical relevance of renal ischemia-reperfusion injury, further studies are necessary to resolve this issue, which may relate to the nature of adenosine being a two-sided sword in ARF. Other possible explanations include discrete differences in the experimental design that have a significant impact. Or we may learn that theophylline can affect systems other than adenosine receptors, which are important in ischemia-reperfusion injury.

X. SUMMARY AND PERSPECTIVES

Adenosine is present in the cytosol of tubular cells and in the renal interstitium of normoxic kidneys (see sect. II). Interstitial concentrations of adenosine under normoxic conditions in rat kidney cortex are ~60 nM. Medullary interstitial adenosine concentrations are about two- to fourfold greater. As in other organs, the renal adenosine tissue levels and interstitial adenosine concentrations increase when the phosphorylation potential falls, causing increased adenosine concentrations in response to excessive transport activity or impaired perfusion. Adenosine is transported into the extracellular space via nucleoside transporters. Adenosine can also derive from extracellular breakdown of ATP, AMP, or cAMP. Extracellular adenosine acts on adenosine receptor subtypes expressed in cell membranes of the kidney (see sect. III) to affect vascular and tubular functions.

An increase in adenosine concentrations leads via activation of adenosine A_1 receptors, primarily in the outer cortex, to sustained afferent arteriolar constriction and a reduction of GFR (see sect. IV). Adenosine acts as a mediator of the TGF, which establishes an inverse relationship between GFR and the NaCl concentration at the macula densa (see sect. V). In the juxtaglomerular apparatus, extracellular formation of adenosine by ecto-5′-nucleotidase (possibly involving prior ATP and/or AMP release from macula densa cells) contributes to the adenosine pool that mediates TGF-induced afferent arteriolar vasoconstriction. The TGF mechanism stablizes the NaCl load to the distal nephron, which facilitates fine regulation of body NaCl balance at these sites. This is illustrated in adenosine A_1 receptor-deficient mice, which lack TGF and show a significant rise in the NaCl load to the nephron segments downstream of the macula densa when proximal tubular load is enhanced or reabsorption is impaired. TGF-induced oscillations of the NaCl load to the tubular and collecting duct system may contribute to the regulation of NaCl balance but may also help to preserve the integrity of the hypoxic medulla. Mice lacking adenosine A_1 receptors also lack TGF-induced oscillations and should be a valuable tool to further evaluate the role of TGF in kidney physiology and pathophysiology.

Adenosine via activation of adenosine A_1 receptors inhibits renin secretion (see sect. VI). An increase in intracellular cAMP is an important stimulator of renin release from juxtaglomerular cells. Part of the cAMP could be released by renin-secreting cells and is extracellularly converted to adenosine, which acts as a negative-feedback control or brake when renin secretion is stimulated. Due to lack of inhibition, the responses to maneuvers that activate the renin system are exaggerated when adenosine A_1 receptors are inhibited or knocked out. Further studies using pharmacological means or knockout mice to inhibit ecto-phosphodiesterase or ecto-5′-nucleotidase, i.e., the enzymes that can extracellularly convert cAMP to adenosine, should provide important insights as to the relevance of the proposed cAMP-adenosine pathway for renin inhibition. Obviously, adenosine A_1 receptors are not critical for the inhibition of renal renin release in response to an increase in dietary NaCl intake or for the

increase in renin release in response to altering the NaCl concentrations sensed by the macula densa from normal to low. In comparison, a macula densa-dependent source of adenosine contributes to renin release inhibition under conditions of high NaCl at the macula densa.

Adenosine exerts distinct direct effects on fluid and electrolyte transport along the tubular and collecting duct system (see sect. VII). Under physiological conditions, endogenous adenosine by activation of adenosine A_1 receptors exerts a tonic stimulation of reabsorption in the proximal tubule. Mice lacking adenosine A_1 receptors also lack the natriuretic responses to the methylxanthines theophylline and caffeine, supporting the concept that blockade of adenosine A_1 receptors, including the proximal tubule, mediates these natriuretic responses. Moreover, selective adenosine A_1 receptor antagonists (which may in addition inhibit K^+ secretion in the distal nephron) are being developed as eukaliuretic natriuretics in Na^+-retaining states. On the other hand, the tonic stimulation of proximal reabsorption by endogenous adenosine lowers the NaCl load to further downstream segments in the medulla, i.e., a region that is characterized by low blood flow and O_2 supply. In contrast to proximal tubule, adenosine by acting on the same receptor subtype can inhibit reabsorption in the medulla, especially in the medullary TAL. Thus endogenous adenosine, the synthesis of which is increased by enhanced NaCl transport, limits via adenosine A_1 receptor activation the oxygen demand in relatively hypoxic nephron segments by directly and differentially affecting reabsorption along the nephron.

Renal medullary hypoxia is an obligatory part of the process of urinary concentration. When O_2 supply is further impaired, however, medullary hypoxic injury can develop. Various mechanisms act in concert to minimize medullary hypoxia. Adenosine-mediated actions like maintaining high proximal reabsorption, inhibiting reabsorption in the medullary TAL, and reducing GFR by the TGF mechanism, when distal NaCl concentrations increase, can be part of these mechanisms (see above). Furthermore, in the deep cortex and medulla, adenosine via adenosine A_{2a} receptor activation causes vasodilation, which increases medullary blood flow and thus medullary oxygenation (see sect. IV). Thus adenosine through distinct actions on the vasculature and tubular transport system contributes to the stabilization of the O_2 demand-to-supply ratio particularly in the renal medulla. Whereas many other factors are likely to also contribute, the outlined evidence supports the concept that adenosine, like in other organs, plays a vital role in the metabolic control of kidney function (see sect. VIII).

In addition to the anti-inflamatory actions, adenosine via its tissue protective role in a metabolic control of kidney function may contribute to the observations that adenosine or adenosine A_1 or A_{2A} receptor activation can exert beneficial effects in renal ischemia-reperfusion injury models (see sect. IX). On the other hand, the unselective adenosine receptor antagonist theophylline can also be beneficial in this setting. This appears contradictory but may relate to the fact that overshooting adenosine-induced vasoconstriction can deteriorate kidney function in ischemia-reperfusion. Along these lines, theophylline and adenosine A_1 receptor antagonists have been found to be useful in the treatment of various forms of acute renal failure in response to nephrotoxic substances including radiocontrast media. Thus pharmacological modulators of adenosine receptors appear to have a potential to contribute to the treatment of forms of acute renal failure including transplantation-related ischemia-reperfusion and nephrotoxic forms, but much has first to be learned on the cellular and molecular mechanisms and the role of the specific adenosine receptors under these conditions.

For further progress in the understanding of adenosine actions in the kidney, it appears also necessary to analyze in the kidney under physiological and pathophysiological conditions *1*) the expression and activity of adenosine-generating, transporting, and degrading enzymes (and assess their functional contribution by including studies in respective knockout models), and *2*) the distribution and expression level of the adenosine receptor subtypes, including studies in humans. The receptor expression is of particular importance since studies involving mice overexpressing adenosine receptors indicated that receptor levels are rate limiting for adenosine actions (369).

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