■ REVIEW ARTICLE

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Succinylcholine-induced Hyperkalemia in Acquired Pathologic States

Etiologic Factors and Molecular Mechanisms

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Lethal hyperkalemic response to succinylcholine continues to be reported, but the molecular mechanisms for the hyperkalemia have not been completely elucidated. In the normal innervated mature muscle, the acetylcholine receptors (AChRs) are located only in the junctional area. In certain pathologic states, including upper or lower motor denervation, chemical denervation by muscle relaxants, drugs, or toxins, immobilization, infection, direct muscle trauma, muscle tumor, or muscle inflammation, and/or burn injury, there is up-regulation (increase) of AChRs spreading throughout the muscle membrane, with the additional expression of two new isoforms of AChRs. The depolarization of these AChRs that are spread throughout the muscle membrane by succinylcholine and its metabolites leads to potassium efflux from the muscle, leading to hyperkalemia. The nicotinic (neuronal) α7 acetylcholine receptors, recently described to be expressed in muscle also, can be depolarized not only by acetylcholine and succinylcholine but also by choline, persistently, and possibly play a critical role in the hyperkalemic response to succinylcholine in patients with upregulated AChRs.

SUCCINYLCHOLINE continues to be the drug of choice for producing paralysis, particularly when there is a need for rapid onset and offset of effect. None of the currently available nondepolarizing relaxants have the pharmacodynamic profile of the depolarizing relaxant, succinylcholine.[1,2] Therefore, succinylcholine continues to be used for urgent tracheal intubation in the perioperative period, in the emergency room, in the intensive care unit, and even outside the hospital during emergency transportation of patients.[3–7] Because succinylcholine has a rapid onset of effect even when administered intramuscularly, it is also used to treat laryngospasm, especially when there is asso-

ciated desaturation, with no intravenous access. In some instances, however, adverse hemodynamic consequences, including death, have been reported with its use. One of the most deleterious side effects of succinylcholine is the acute onset of hyperkalemia and the cardiovascular instability associated with its administration in certain susceptible patients.

Patients with congenital muscular dystrophies are susceptible to hyperkalemia and rhabdomyolysis with succinylcholine.[8] The etiology of this response, however, is unclear. The acquired disease states that are associated with succinylcholine-induced hyperkalemia were first reviewed in 1975.[9] The etiologic factors contributing to this side effect in certain individuals were comprehensively updated approximately a decade ago.[10] Brief attention to this topic was given in a recent review on the "neurobiology of neuromuscular junction."[11] Classic acquired conditions that have the potential to result in acute lethal hyperkalemia with succinylcholine administration are enumerated in table 1. In each of these conditions listed, there is an up-regulation (increase) of muscle nicotinic acetylcholine receptors (AChRs), which when depolarized with succinylcholine leads to efflux of intracellular potassium into the plasma, leading to acute hyperkalemia. Several recent clinical reports continue to implicate distinct and varied pathologic states that give rise to hyperkalemia with succinylcholine. Some of the conditions purported to cause hyperkalemia with succinylcholine have included gastrointestinal mucositis,[12] necrotizing pancreatitis,[13] catatonic schizophenia,[14] meningitis,[15] and purpura fulminans.[16] Despite the claim (actual or implied) that each of these varying pathologic states is a potential independent risk factor for hyperkalemia with succinylcholine, it is evident that one or more of the etiologic factors previously enumerated in table 1 were concomitantly present, leading to the up-regulation of AChRs and therefore making them susceptible to hyperkalemia with succinylcholine.

There is now evidence that an isoform of AChR, neuronal (nicotinic) α7AChR, previously not described in muscle, is also expressed and up-regulated in muscle during development and with denervation.[17] There is preliminary evidence to suggest that these α7AChRs may

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Table 1. Pathologic Conditions with Potential for Hyperkalemia with Succinylcholine

Upper or lower motor neuron defect
Prolonged chemical denervation (*e.g.*, muscle relaxants, magnesium, clostridial toxins)
Direct muscle trauma, tumor, or inflammation
Thermal trauma
Disuse atrophy
Severe infection

All of these conditions have the potential to up-regulate (increase) acetylcholine receptors.

also be expressed in other conditions listed in table 1. The α7AChR can be depolarized not only by acetylcholine or succinylcholine, but also by their metabolite, choline, strongly and persistently (without desensitization),[18] with a capability to exaggerate the intracellular potassium efflux into plasma in any pathologic state, where α7AChRs are up-regulated. This review reaffirms the unifying hypothesis that conditions with increases in AChRs have the potential to cause a hyperkalemic response with succinylcholine and provides an update on the biochemical and molecular pharmacology of AChRs in muscle with new insights into the molecular mechanisms for hyperkalemia with succinylcholine.

Conditions That Increase AChRs in Skeletal Muscle

Functional or Anatomical Denervation

Lower or upper motor neuron injury is the classic condition where up-regulation of AChRs has been consistently observed.[9-11] Despite previous warnings about the use of succinylcholine in patients with upper or lower motor neuron lesions, its use in these situations continue. There is an account of the use of succinylcholine, to decrease myogenic activity during the performance of electroencephalography in a patient with stroke, that resulted in hyperkalemia.[19] Another report of hyperkalemia with succinylcholine implicating pancreatitis as the etiologic factor actually had an upper motor neuron lesion of several weeks' duration.[13] Polyneuropathy and myopathy of critical illness is a disease of multiple etiology and is associated with both sensory and motor deficits.[20,21] Therefore, in critical illness–induced neuromyopathies, the muscle and the AChRs would behave as if they were denervated. It is, therefore, not surprising that one would see hyperkalemia with succinylcholine in the presence of critical illness polyneuropathy.[22] Chronic ischemia (peripheral vascular disease), renal failure, and diabetes produce neuropathies of varying degrees, depending on the severity and duration of the illness. All of these diseases have the propensity for hyperkalemia with succinylcholine, because of the neuropathy-induced denervation.[23]

In both upper and lower motor neuron lesions, the

AChRs spread well beyond the neuromuscular junction (NMJ) and are present throughout the muscle membrane. Supersensitivity to AChR agonists (acetylcholine or succinylcholine) is observed throughout the muscle membrane.[9,24] The increase in AChRs after denervation is more profound and occurs more quickly than with simple immoblization.[24,25] This increase in receptor number can be confirmed by radiolabeled α-bungarotoxin (cobra toxin), which covalently binds to all muscle AChRs, irrespective of isoform. Chemical denervation occurs when neuromuscular relaxants are used for prolonged periods.[26,27] The up-regulation of AChRs associated with the use of muscle relaxants is a predictable response. Classic receptor theory indicates that during the chronic presence of a competitive antagonist (or conditions that decrease concentrations of transmitter), there is up-regulation of that receptor.[10] Up-regulation is typically associated with increased sensitivity to agonists and resistance to antagonists. These typical responses have been verified in many receptor systems, including the AChR, where increased sensitivity to succinylcholine and resistance to nondepolarizing relaxants were demonstrated.[10,26,27] Therefore, the chemical denervation and increase in AChRs associated with prolonged administration of muscle relaxants can lead to hyperkalemia with succinylcholine.[26,28] The coadministration of muscle relaxants in association with another pathologic condition that up-regulates AChRs (*e.g.*, burn injury, immobilization) can magnify the increase in AChRs even further, over and above that caused by the pathologic condition alone.[26,29]

Simple Immobilization

Examples of immobilization include confinement in bed or wheelchair, pinning of joints, and plaster casting of single limb or total body (spica). Severe critical illness often results in immobilization of some or most of the skeletal muscles for varying periods because of disease-induced factors. Although the nerve itself is not anatomically severed during this time, the immobilized muscle behaves as if it were denervated.[30-32] Within 3–5 days of immobilization, the muscle fibers become atrophied, and the NMJ begins to show degenerative changes (nerve terminal disruption, terminal nerve sprouting, multi-innervations of the NMJ, exposed or lost junctional folds).[30] Although there is no associated apparent disruption of nerve function, the biochemical feature of classic denervation, up-regulation of AChRs and spread of receptors beyond the NMJ, is observed.[30-32] This up-regulation of AChRs that occurs with immobilization can be seen as early as 6–12 h[33,34] and is transcriptionally (messenger ribonucleic acid)[32,33] or posttranscriptionally mediated[34] but does not reach critical levels to cause hyperkalemia as early as 24–72 h after immobilization. Although immobilization itself up-regulates AChRs, concomitant pathologic states or iatrogenic ma-

nipulations can accentuate this up-regulation. Examples of the latter would include use of drugs such as magnesium sulfate[35] or muscle relaxants.[25–27] Magnesium, among other effects, also inhibits the release of acetylcholine at nerve endings, which by itself can up-regulate AChRs.[35] Succinylcholine hyperkalemia has been observed as early as 5 days of immobilization in association with meningitis.[15] Therefore, the concomitant presence of one or more pathologic states, with immobilization, which independent of each other can up-regulate AChRs, leads to quicker and more profound increase in receptor number with a potential for hyperkalemia at an earlier period of time.

Infection and Burn Injury

Previous reports have indicated that chronic infection is a risk factor for succinylcholine-induced hyperkalemia.[36,37] Infection with *Clostridium botulinum* and *tetani*, causing botulism and tetanus, have well established effects on the NMJ.[38,39] These exotoxins produce paralysis by binding to cleavage proteins that control the release of acetylcholine, leading to muscle paralysis and a denervation-like state. Although the nerve itself is not severed, the decreased release of acetylcholine produced by clostridial toxins and the associated paralysis leads to the up-regulation of AChRs.[25,38,39] Therefore, the use of succinylcholine in patients with tetanus can result in hyperkalemia. Infection by botulinum is not uncommon among drug abusers, and succinylcholine hyperkalemia has been reported during clostridial sepsis.[40,41] Therefore, the use of succinylcholine to rapidly secure an airway in a long-term drug abuser does have the potential for hyperkalemia. Parenthetically, botulinum toxin (Botox®; Allergen Inc., Irvine, CA), now extensively used as a therapeutic agent for many muscle disorders, does not usually produce generalized denervation in the recommended doses.[42] The use of muscle relaxants either to prevent the muscle spasms of tetanus or to facilitate mechanical ventilation in the intensive care unit aggravates the up-regulation of AChRs produced by the clostridial infection or disease-induced immobilization. These patients, therefore, have the propensity for hyperkalemia with succinylcholine, if it is used subsequently.

In contrast to clostridial toxins, it is unclear whether infection with other bacterial or viral agents can effect changes in receptor number to critical levels to produce hyperkalemia, particularly in the absence of immobilization. An inflammatory or infectious state induced by repeated exposure to endotoxin or a single injection of *Corynebacterium parvum* in animals that were allowed to move freely did not increase AChR number.[43,44] Repeated (three times) injections of *C. parvum* over 12 days, with and without single limb immobilization, produced modest increases of AChR number but did not produce a hyperkalemic response to succinylcholine (Helming M, Fink H, Unterbuchner C, Martyn JAJ, Blob-

ner M, unpublished observations, June 2005). To the contrary, infection may, in fact sometimes, decrease AChR number (in the absence of immobilization).[45] The reports of hyperkalemia in patients with infection[36,37] may be related to the up-regulation of AChRs induced by total body immobilization with and without muscle relaxants acting in consort with the infection itself. Accordingly, infection together with immobilization, as seen in the intensive care unit, may be comorbid factors that would accentuate the up-regulation of AChRs and lead to hyperkalemia with succinylcholine.

As indicated previously, sepsis or systemic inflammatory response syndrome, however, is known to be associated with both sensory and motor demyelinating neuropathies.[20,21] The motor neuropathy no doubt will lead to AChR spread, with a chance for hyperkalemia with succinylcholine. The burn injury–related increase of AChRs is probably related to inflammation and local denervation of muscle.[46] The up-regulation of AChRs at sites distant from burn, if it occurs, is most likely related to the concomitant immobilization, because systemic distant effects on AChRs are not consistently observed.[46,47] Major third-degree burn involving extensive body surface area may, however, up-regulate AChRs throughout the body because of its extent and direct inflammation/injury to muscle, even in the absence of infection. However, hyperkalemia after burn injury to a single limb (8% body surface area) has been observed, indicating that burn size alone is not the only contributing factor.[48] Superimposition of infection or sepsis may accentuate the burn- or immobilization-induced increase of AChRs even further. Exogenous steroids, sometimes used to treat critically ill septic and asthmatic patients, by itself does not increase receptor number.[49] It may be of interest to note that steroidal muscle relaxants (pancuronium, vecuronium, rocuronium), sometimes used in the intensive care unit to facilitate mechanical ventilation, do not have a steroidal effect and do not seem to potentiate the effects of exogenous steroids.[50]

Nomenclature of Nicotinic AChRs, Pharmacology, and Control of Expression in Muscle

Nicotinic AChRs, named for their ability to bind to the tobacco alkaloid, nicotine, are members of the neurotransmitter gated ion channels that mediate excitatory neurotransmission at the NMJ, autonomic ganglia, and selected synapses of the brain and spinal cord.[51,52] Diverse genes encode the heterogenous AChRs, and the ion channel is formed of multiple subunits (multimers). To date, 17 nicotinic acetylcholine subunit genes have been cloned from vertebrates and include $\alpha 1$–$\alpha 10$ and $\beta 1$–$\beta 4$ subunits and one each of δ, γ, and ε subunits. Specific information about the molecular organization
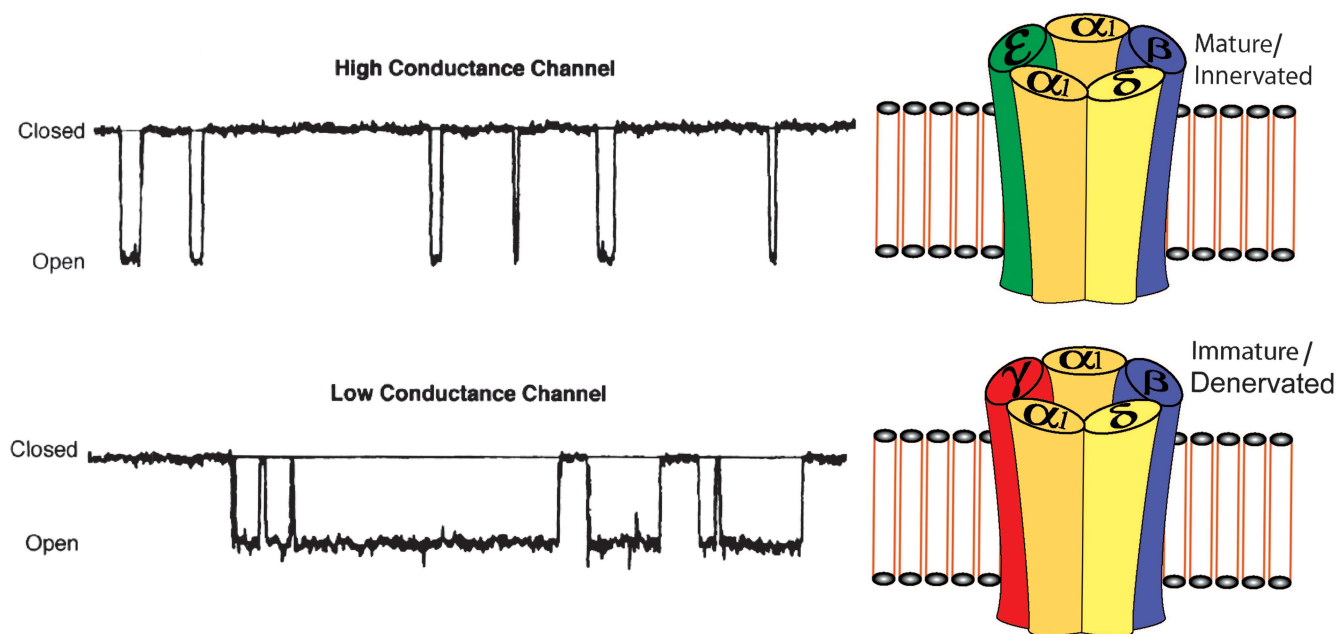
Fig. 1. Sketch of muscle acetylcholine receptor channels (*right*) and tracings of cell patch records of receptor channel openings (*left*). The mature, innervated, or junctional receptor consists of two $\alpha 1$ subunits, and one each of the $\beta 1$, δ, and ε subunits. The immature, extrajunctional or fetal form consists of two $\alpha 1$ subunits and one each of the $\beta 1$, δ, and γ subunits. The ε subunit is therefore substituted by the γ subunit in the immature receptor. The subunits are arranged around the central cation channel. The mature isoform containing the ε subunit shows shorter open times and high-amplitude currents; hence, it is called *high-conductance channel*. The immature isoform containing the γ subunit is called *low-conductance channel* because it shows long open times and low-amplitude currents. The immature receptors can be depolarized with smaller concentrations of acetylcholine or succinylcholine. Therefore, they can be depolarized more easily even with decreasing concentrations of succinylcholine during its continued metabolism after systemic administration. The fact that these immature channels remain open for a longer time and are up-regulated in muscles in certain pathologic states increases the chance that intracellular potassium ions will leak out and increase the plasma levels of potassium.

and function of AChRs in the central and peripheral nervous system is lacking, but those in muscle are better characterized.

Conventional Muscle AChRs

The schematic in figure 1 illustrates known arrangements of the subunits constituting the well-studied (conventional) muscle AChRs, the molecular weight of which is approximately 250,000 Da. In the mature adult-innervated NMJ, the AChRs are located only in the junctional area. The AChR ion channel on the muscle membrane transmits cations (sodium and calcium) into and (potassium) out of the cell, during depolarization and repolarization, respectively, and is formed of five subunit (pentamer) proteins consisting of two $\alpha 1$ subunits and one each of the β, δ, and ε subunits. This AChR channel is referred to as a "mature," "innervated," or "ε-containing" channel. The density of the junctional (mature) AChRs is quite high, approximately 5 million per junction, in the adult mature junction. In the fetus (before innervation) or after denervation syndromes (table 1), the receptors are not clustered (localized) in the junctional area only, but are spread throughout the muscle membrane (extrajunctional receptors). These extrajunctional receptors occupy the whole muscle membrane, and their number varies depending on the pathologic

state and its duration. Their density, however, never reaches that of the junctional area. These AChRs, called "immature," "fetal," or "extrajunctional" type, are formed of two $\alpha 1$ subunits and one each of the $\beta 1$, δ, and γ subunits, differing from the mature channel only in the substitution of the γ for the ε subunit.

Each AChR subunit protein consists of 400–500 amino acids. The receptor protein complex passes entirely through the membrane and protrudes beyond the extracellular surface of the membrane and also into the cytoplasm (fig. 1). The binding site for agonists and antagonists is on each of the α subunits located near 192–193 amino acid positions.[10,11] During immobilization of muscle also, whether it is produced by simple muscle inactivity or chemically, iatrogenically (*e.g.*, pinning), or pathologically induced, the AChRs qualitatively and quantitatively behave as if they are denervated.[24-32] The most common chemical agents producing immobilization and denervation are the neuromuscular relaxants. Another therapeutic chemical causing denervation is botulinum toxin (Botox®), used for treating muscle disorders.[42] Magnesium has similar effects on the nerve, preventing the release of acetylcholine.[35] Direct electrical stimulation of the muscle, even in the absence of nerve function or nerve-evoked muscle contraction, attenuates the spread of AChRs, underscoring the impor-

Choline-induced depolarization in α7 AChR
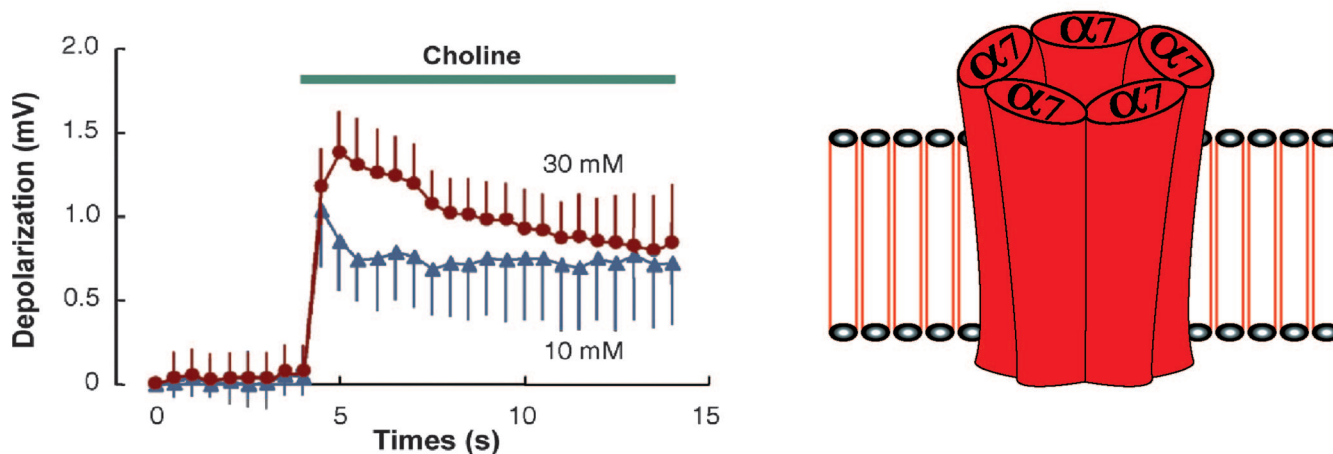

Fig. 2. Sketch of an α7 acetylcholine receptor (AChR) (*right*) expressed in muscle after denervation and its pharmacologic property during depolarization by choline (*left*). The α7AChR is a homomeric channel composed of five α7 subunits (pentamer) whose channel is responsive to (opened by) acetylcholine and choline, and binds to nicotine. The chemical agent, α-conotoxin GI, was used to specifically inhibit muscle α1, β1, δ, and ε/γ AChRs. The α7AChRs are not inhibited by α-conotoxin GI, thus allowing the study of α7AChRs in muscle (*left*). Of note, choline, the metabolite of acetylcholine and succinylcholine, is a full agonist of the α7AChR with little desensitization even with continued (15 s) exposure to choline (*left*). Note that the depolarization can be increased with higher (30 *vs.* 10 mM) concentrations of choline, and the depolarization persists as long as choline is applied. This phenomenon has the potential to continue efflux of intracellular potassium into the synapse, extracellular fluid, and plasma. Redrawn from Tsuneki *et al.*[18]; used with permission from Blackwell Publishing.

tance of muscle electrical activity in the control of AChRs.[24,34,53]

The changes in subunit composition (γ *vs.* ε) in the conventional muscle AChRs confer certain changes in the electrophysiologic (functional), pharmacologic, and metabolic characteristics.[10,11] The mature receptors are metabolically stable, with a half-life of approximately 2 weeks compared with less than 24 h in the immature receptor. The changes in subunit composition also alter the sensitivity or affinity of the receptor for specific ligands or both. Depolarizing or agonist drugs, such as succinylcholine and acetylcholine, depolarize immature receptors more easily and therefore can efflux intracellular potassium at lower concentrations of these agonists; only one tenth to one hundredth of doses that depolarize mature receptors effect depolarization in immature AChRs.[9,24,54] Immature receptors have a smaller single-channel conductance and a 2- to 10-fold longer mean channel open time (fig. 1). That is, once depolarized, the immature channels stay open for a longer time.

Neuronal AChRs in Muscle

Quite in contrast to the conventional muscle AChRs consisting of α1, β1, δ, and ε/γ subunits described above, receptors formed of α7AChR subunits have recently been found in skeletal muscle during development and denervation.[17,18] These α7AChRs are homomeric (*i.e.*, formed of the same subunits) channels arranged as pentameres (fig. 2). Ligand (drug) binding pockets are thought to be formed at negative and positive faces of the α7-subunit assembly interphases. As expected, the endogenous agonist, acetylcholine binds to α7AChRs, and each of the five subunits has the potential to bind acetylcholine or succinylcholine molecules.[51,52,55] Other agonists, including nicotine and choline, and antagonists (muscle relaxant, pancuronium and cobra toxin, α-bungarotoxin) also bind to the α7AChR.[18]

The α7AChRs display unusual functional and pharmacologic characteristics compared with the conventional muscle (α1, β1, δ, ε/γ) AChRs or the neuronal (brain) α7AChRs. Choline, a precursor and metabolite of acetylcholine (and succinylcholine), is an extremely weak agonist (EC_{50} 1.6 μM) of the conventional muscle AChRs but is a full agonist of the muscle α7AChRs (0.26 mM); *i.e.*, concentrations of choline that do not open the conventional AChR channels will open the α7AChR channels.[18] Furthermore, no desensitization of the α7AChR occurs even during the continued presence of choline (fig. 2),[18] thus allowing a greater chance for potassium to efflux from within the cell (approximately 145 mEq/l in cell) to the extracellular space including plasma (approximately 4.5 mEq/l) down its concentration gradient. The chemical α-conotoxin GI specifically inhibits the conventional (mature and immature) AChRs in muscle but does not inhibit α7AChRs. The muscle α7AChRs are different from neuronal (autonomic ganglia and brain) α7AChRs in that the former are not strongly inhibited by the selective antagonist of neuronal α7AChR, methylcaconitine. The α7AChRs expressed in neuronal tissue are also desensitized readily with choline,[56] a feature that contrasts with muscle α7AChRs, which do not desensitize with choline.[18] The α7AChR in

muscle also has a lower affinity for its antagonists, including pancuronium and α-bungarotoxin; higher concentrations of these drugs are, therefore, required to block agonist-induced depolarization in the α7AChR *versus* the conventional muscle AChRs ($\alpha1$, $\beta1$, δ, ε/γ).[18] In the conventional AChRs, the binding of even one of the $\alpha1$ subunits by an antagonist results in inactivation of that receptor, because acetylcholine needs both α subunits of the AChR for its activation. In the α7AChR, however, even when three subunits are bound by an antagonist (*e.g.*, muscle relaxant), there are two other subunits still available for binding to agonist and depolarization. This feature may account for the resistance of α7AChR, compared with conventional AChRs, to the blocking effects of drugs such as pancuronium.[18]

The clinical pharmacology of the muscle α7AChR has not been studied yet, but the basic pharmacology provides some insight into succinylcholine-related hyperkalemia. Chemical or physical denervation of muscle not only results in up-regulation and qualitative (ε-subunit $\rightarrow$ γ-subunit expression) changes in AChRs, but also up-regulates the α7AChRs in muscle. Preliminary (Kaneki M, Martyn JAJ, unpublished data, June 2005) evidence suggests increased protein expression (by Western blotting) of α7AChRs in burn injury also. Succinylcholine, a synthetic analog of acetylcholine consisting of two molecules of acetylcholine joined together, is capable of depolarizing not only the conventional muscle AChRs, but also the α7AChRs found in muscle[55] (fig. 3). In addition, the metabolite of succinylcholine, choline, can depolarize α7AChRs with little desensitization. The depolarizing effects of succinylcholine and choline on the up-regulated α7AChRs result in continued leak of intracellular potassium with flooding of extracellular fluid including plasma, leading to hyperkalemia. The effect of choline, particularly on the α7AChRs, may explain the persistence of hyperkalemia that is seen in some patients well beyond the paralytic action of succinylcholine (vide fig. 2 and infra).

Synthesis and Stabilization of the AChRs

This subject has been recently reviewed in detail,[11,33] but a brief description is provided. The trophic function of the nerve and the associated electrical activity is vital for the development, maturation, and maintenance of neuromuscular function. Shortly after the motor nerve axon grows into the developing muscle, these axons bring nerve-derived signals (*i.e.*, growth factors), including agrin, that are key to maturation of muscle and NMJ.[10,11,33,53] Agrin is a protein released by the nerve that stimulates postsynaptic differentiation by activating muscle-specific kinase (MUSK), a tyrosine kinase expressed selectively in muscle. With signaling from agrin, the AChRs, which have been scattered throughout the muscle membrane, cluster at the area immediately beneath the nerve. Agrin, together with other growth factors called neuregulins, also induce the clustering of other critical muscle-derived proteins, all of which are necessary for maturation and stabilization of the AChRs at the NMJ. Sometime after birth, all of the receptors are converted to mature ε-subunit–containing AChRs. Although the mechanism of this change is unclear, a neuregulin (growth factor) called ARIA (for acetylcholine receptor-inducing activity), which binds to ErbB receptors, seems to play a role.[57] No information is available regarding the growth factors that control the expression of α7AChRs, except that conditions that increase expression of the γ-subunit–containing AChRs also seems to increase α7AChRs. Therefore, signaling from agrin, and neuregulins may be important for suppression of α7AChRs.

Molecular Pharmacologic Bases for Hyperkalemia with Succinylcholine

Acetylcholine receptors in the electrically excitable innervated muscle cluster and localize around the nerve at the NMJ due to trophic factors released from the nerve. The nerve-evoked muscle contractions stabilize this clustering.[33,53] When succinylcholine is administered to healthy patients, it depolarizes the receptors, which are present only at the NMJ, and the resulting efflux of intracellular potassium ions is therefore limited to the junctional area. Despite the high density of AChRs at the NMJ, this depolarization results in a change in plasma potassium concentrations of approximately 0.5–1.0 mEq/l. Loss of muscle excitation (contraction), for whatever reason (denervation, immobilization, muscle relaxant therapy, toxins), leads to a loss of clustering and the spread of AChRs throughout the whole muscle membrane. The extent of the up-regulation of AChRs (2- to 100-fold) is determined by the severity and duration of the pathologic state. It is important to note, however, that although the density of AChRs at the extrajunctional areas is very much less than that at the junctional area, the surface area of the muscle itself is so large that the AChR numbers are markedly increased on the muscle membrane.[24,53] These up-regulated receptors in the extrajunctional area consist of immature ($2\alpha1$, $\beta1$, δ, γ) and $\alpha7$ AChRs. The proportion of each of these receptor subtypes (γ *vs.* $\alpha7$) in the affected muscle is unknown, but the total AChR number dramatically increases compared with the innervated muscle. Acetylcholine released during nerve-evoked muscle contraction is able to activate only junctional receptors, because the transmitter is rapidly metabolized by acetylcholinesterase enzyme present in the perijunctional area. This depolarization produced by acetylcholine, therefore, does not extend beyond the junctional receptors, even in denervation/immobilization/inflammation states. However, in the pathologic states, where the AChRs are up-regulated and occupy all of the muscle membrane, the systemically carried succinylcholine
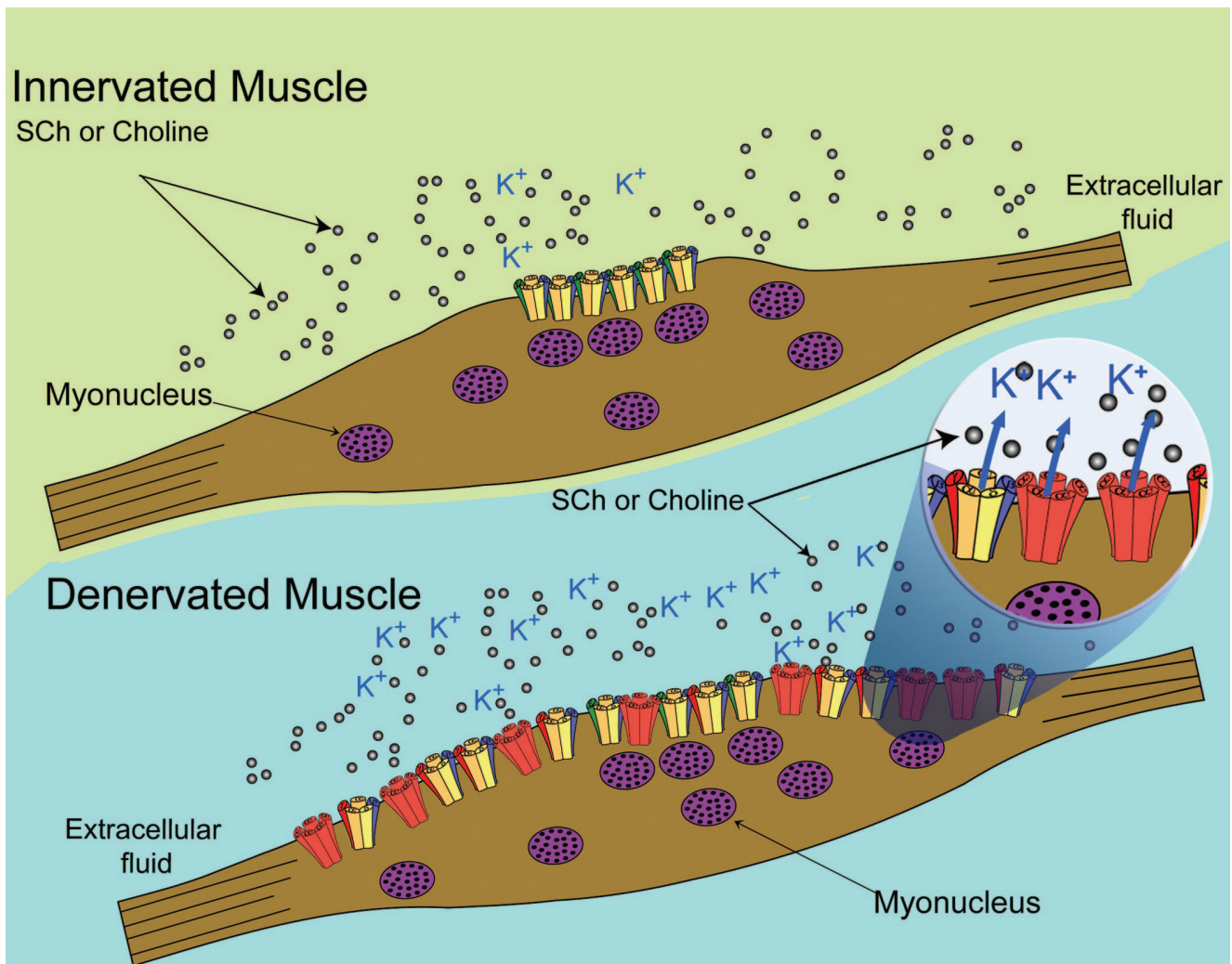
Fig. 3. Schematic of the succinylcholine (SCh)–induced potassium release in an innervated (*top*) and denervated muscle (*bottom*). In the innervated muscle, the systemically administered succinylcholine reaches all of the muscle membrane but depolarizes only the junctional (α1, β1, δ, ε) receptors because acetylcholine receptors (AChRs) are located only in this area. With denervation, the muscle (nuclei) expresses not only extrajunctional (α1, β1, δ, γ) AChRs but also α7AChRs throughout the muscle membrane. Systemic succinylcholine, in contrast to acetylcholine released locally, can depolarize all of the up-regulated AChRs leading to massive efflux of intracellular potassium into the circulation, resulting in hyperkalemia. The metabolite of succinylcholine, choline, and possibly succinylmonocholine can maintain this depolarization *via* α7AChRs enhancing the potassium release and maintaining the hyperkalemia.

is able to depolarize all of the AChRs (not only junctional receptors), causing efflux of potassium from all of the AChRs throughout the muscle membrane (fig. 3). Furthermore, in contrast to acetylcholine, because succinylcholine is metabolized more slowly (10–20 min), sustained depolarization of the 2α1, β1, δ, ε/γ, and α7 AChRs occurs, exaggerating the potassium release.

There are additional factors that may compound the exaggerated release of potassium from these AChRs. The immature receptor, which has a longer open channel time when depolarized, has a greater potential for sustaining a more prolonged potassium leak. Because these immature AChRs can be depolarized with smaller-than-normal concentrations of succinylcholine,[9,24,54] the depolarization can continue to occur despite continued metabolic breakdown and lower concentrations of succinylcholine. Most importantly, the metabolic break-

down product of succinylcholine, choline, is a strong agonist of α7AChR. Each molecule of succinylcholine releases two molecules of choline. The usual 1.5-mg/kg dose of succinylcholine (approximately 100 mg in the adult), therefore, is able to release approximately 0.56 mM choline. This choline concentration is well outside the physiologic range,[58] and sufficient to continue to activate α7AChRs, with release of more potassium into the circulation. (As indicated previously, the EC_{50} for muscle α7AChR is 0.26 mM.[18]) Because the α7AChRs do not desensitize with choline (fig. 2), the α7AChR channel can continue to be depolarized (open) with persistence of hyperkalemia for a prolonged period. It is conceivable that the other metabolite of succinylcholine, succinylmonocholine, would have the same effect on the α7AChRs, but this has not been studied relative to α7AChRs. The up-regulation of

Arterial K⁺   Time

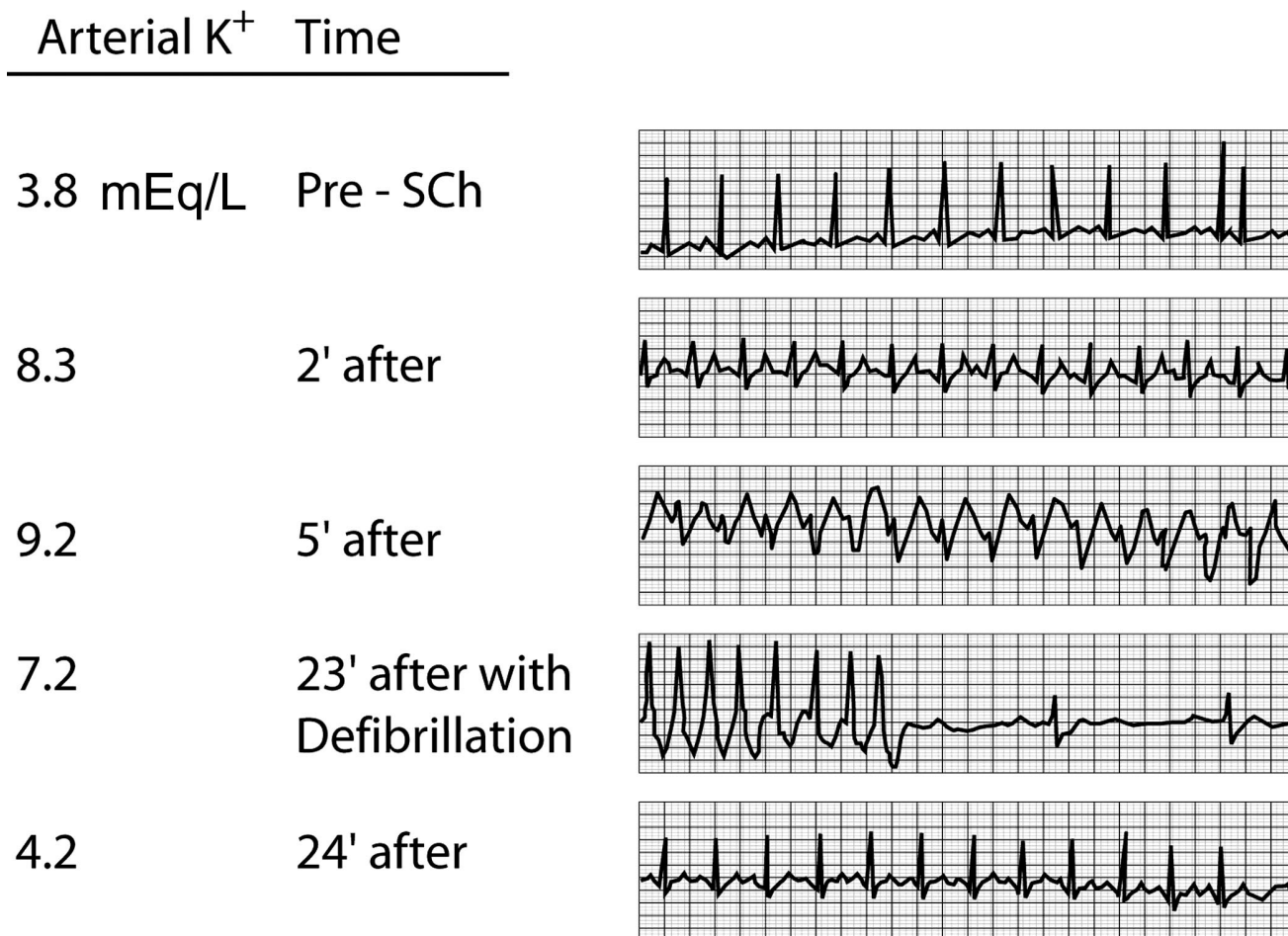| Arterial K^+	Time	
3.8 mEq/L	Pre - SCh	
8.3	2' after	
9.2	5' after	
7.2	23' after with Defibrillation	
4.2	24' after	

Fig. 4. The electrocardiogram and serum potassium levels after succinylcholine (SCh) in a patient 1 month after massive trauma. The release of potassium reaches its peak in 2–5 min and can persist for long periods. Ventricular fibrillation, ventricular tachycardia, wide QRS complexes, and/or peaked T waves can persist as long as potassium levels are high. Defibrillation is ineffective in the presence of high potassium levels. High levels of calcium may revert this, and repeat doses may be required while monitoring the response to electrocardiography. Redrawn from Mazze *et al.*[67]; used with permission.

α7AChRs may also lead to resistance to nondepolarizing relaxants, such as pancuronium; the concentration of pancuronium required to attenuate choline-evoked depolarization was higher in the presence of α7AChR than with conventional AChRs.[18] Therefore, usual doses of pancuronium, or any other nondepolarizing muscle relaxant administered before succinylcholine, would not ablate the hyperkalemic response to succinylcholine.[9]

Diagnosis and Treatment of Hyperkalemia with Succinylcholine

Electrocardiographic changes in association with cardiovascular instability, occurring within 2–5 min after succinylcholine administration, should alert the caregiver to a tentative diagnosis of succinylcholine-induced hyperkalemia. Hyperkalemia can be classified as mild (K^+ 5.5–6.0 mEq/l), moderate (K^+ 6.1–6.9), and severe (K^+ > 7.0).[59] The electrocardiographic changes are usually proportional to the serum potassium levels in approximately 64% of patients (fig. 4). The electrocardio-graphic changes include tall T waves greater than 5 mm (K^+ 6–7), small broad or absent P waves, wide QRS complex (K^+ 7–8), sinusoidal QRST (K^+ 8–9), and atrioventricular dissociation or ventricular tachycardia/fibrillation (K^+ > 9).[59] Although peaked T waves may be seen at serum potassium levels as low as 6 mEq/l, it is not until the level reaches 8 mEq/l or more that the electrocardiogram is consistently diagnostic of hyperkalemia. Cardiovascular instability usually occurs at a serum potassium level equal to or greater than 8 mEq/l, although values of more than 11 mEq/l have been recorded without cardiovascular complications.[60,61] Therefore, hyperkalemia, even in the presence of an abnormal electrocardiogram, may go unnoticed, or electrocardiographic changes may not always be present with hyperkalemia.[60,61] Differential diagnosis of the new-onset QRST changes should include acute pericarditis, left bundle branch block, pulmonary embolism, Prinzmetal angina, and acute myocardial infarction.[62] Although the diagnosis of acute hyperkalemia is confirmed by the measurement of serum potassium levels, treatment should be

initiated based on history (succinylcholine administration in susceptible pathologic state), and electrocardiographic or cardiovascular changes.

Severe hyperkalemia, particularly with cardiovascular collapse, is a life-threatening condition. Therefore, treatment of the hyperkalemia and the associated cardiovascular compromise needs immediate attention. Although frequent serial measurements may be accurate in this critical setting, the fastest measure of efficacy of therapy is the electrocardiogram. There are no studies examining the treatment of acute hyperkalemia induced by succinylcholine. Experience in the treatment of hyperkalemia comes from management of this condition in end-stage renal disease. The subject has been reviewed recently.[63] Whenever there is electrocardiographic evidence of hyperkalemia including early signs of it (peaked T wave), multipronged therapy should be initiated simultaneously.

Approaches to treatment should include antagonizing K^+ effects on cardiac conduction and shifting K^+ from extracellular fluid to intracellular fluid. Calcium salt (chloride or gluconate) should be administered intravenously with continuous electrocardiographic monitoring. Calcium directly antagonizes hyperkalemia-induced depolarization of resting membrane potential. Calcium, among other electrophysiologic effects, increases the threshold potential, thereby restoring the gap between the resting membrane potential and threshold potential in the heart, and preventing spontaneous depolarization.[61] The membrane stabilizing effect is seen even in the presence of hyperkalemia. The recommended dose is 10 ml (1–2 ampules) of 10% calcium gluconate (or chloride) administered as a slow bolus over 2–3 min.[63] The dose in children is 0.5 ml/kg.[59] Calcium, even when effective, may require several repetitive doses because its effect dissipates in 15–30 min. Accordingly, the dose should be titrated based on electrocardiographic and cardiovascular response. Because calcium chloride is more likely to cause tissue necrosis with extravasation, calcium gluconate is increasingly used.

Agents that promote the cellular uptake of potassium include insulin with glucose, catecholamines, and sodium bicarbonate. Acidosis enhances the release of potassium from the cell. Repeated doses (1–3 ml/kg) of sodium bicarbonate (8.4%) to correct the acidosis may be useful, although its effectiveness in the acute setting has been questioned.[63] Alkalization of plasma decreases levels of ionized calcium. This should be kept in mind, and the calcium administration should be more liberal. Glucose (50 ml dextrose, 50%) together with 10 U regular insulin will facilitate the redistribution of potassium into the cell. In children, a glucose load of 0.5 g/kg (2.5 ml/kg dextrose, 50%) with 0.05 U/kg insulin is recommended.[59] Insulin enhances cellular uptake of potassium by stimulating sodium–potassium adenosine triphosphatase pump and is independent of the hypoglycemic effect. The effect of insulin takes at least 10 min, and peak effect takes 30-60 min.[63] β-Receptor ago-

nists, such as epinephrine, will not only help with cardiopulmonary resuscitation but also drive the potassium intracellularly; α-adrenoceptor agonists are not considered useful for the decrease of extracellular potassium.[64] β_2-Adrenoceptor agonists *via* nebulizer (*e.g.*, albuterol) have been used in renal patients with hyperkalemia. The effect of catecholamines can be seen as early as 3–5 min, but peak effect takes 30 min.[63]

The hyperkalemia to succinylcholine is dose dependent. Extremely small doses of succinylcholine (0.1 mg/kg) in denervation states can cause paralysis with no hyperkalemia.[65] Despite this (single) observation, it is inadvisable to use succinylcholine in susceptible patients, because the paralytic and hyperkalemic responses are unpredictable. In most patients, the succinylcholine-induced hyperkalemia lasts less than 10–15 min.[9,66] In some instances, however, the reversal to normokalemia may take much longer (fig. 4).[67] Therefore, cardiopulmonary resuscitation should be continued as long as necessary. Why the hyperkalemia subsides in 10–15 min in some but persists longer in others is unclear. Basic studies indicate that the hyperkalemia induced by succinylcholine is proportional to the AChR number (fig. 5), and the expressions of these receptors are proportional to their messenger ribonucleic acid expression levels.[25,31,32,46] The higher the up-regulation is, the more profound will be the hyperkalemia. If the up-regulation of AChRs is limited to some but not all muscles, redistribution (dilution) of potassium within the extracellular fluid will result in shorter-lived hyperkalemia. If many muscles are involved, the potassium increase will be more acute and profound and will last longer. Concomitant rhabdomyolysis may aggravate this. Lack of redistribution and decreased reuptake by muscle due to cardiovascular collapse may explain the persistence for longer periods. Another plausible speculation for the persistence of the hyperkalemia may be related to the continued effects of succinylcholine and choline on the $\alpha7$AChRs, which can continue to leak potassium without desensitization.[18] The decreased pseudocholinesterase activity seen in critical illness[68] may contribute to the persistence of depolarizing effects of succinylcholine and succinylmonocholine and to the morbidity.

Onset and Duration of Susceptibility to Hyperkalemia with Succinylcholine

The up-regulation of AChRs at the muscle membrane has been demonstrated within hours of denervation, the most severe form of immobilization. Even in the absence of denervation, immobilization with and without the use of muscle relaxants can lead to redistribution from the NMJ and up-regulation of AChRs in the extrajunctional areas as early as 6–12 h.[33,34] This up-regulation is not high enough to cause hyperkalemia with succinylcho-
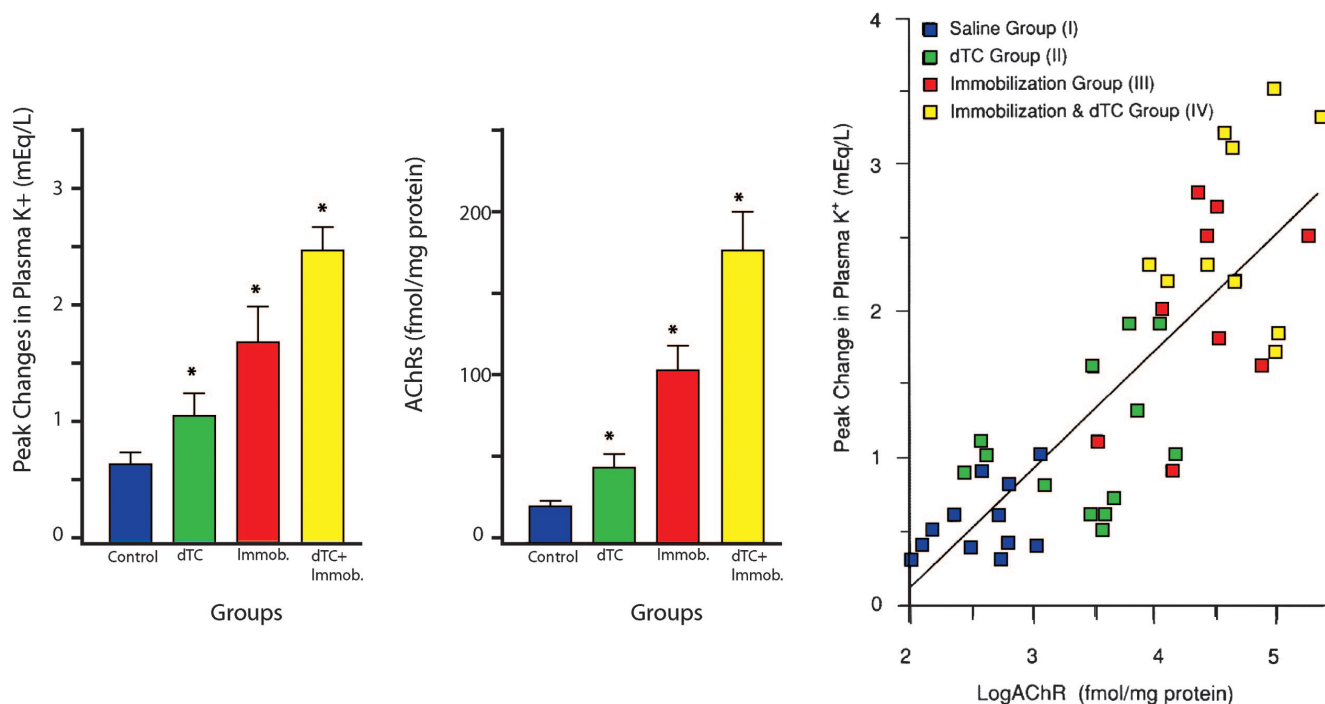
Fig. 5. The relation between membrane acetylcholine receptors (AChRs) and potassium release after succinylcholine. Potassium response to succinylcholine was assessed in normal, lower limb plaster cast–immobilized, nonparalyzed (mobile) animals receiving *d*-tubocurarine (dTC), and lower leg plaster cast–immobilized animals also receiving subparalytic doses of dTC. Each of these perturbations was associated with graded increases in AChR number. The potassium response to succinylcholine correlated with AChR number. The importance of each of the subunit isoforms in the hyperkalemic response to succinylcholine was not characterized. Redrawn from Yanez and Martyn[26]; used with permission.

line even at 24–48 h of immobilization/denervation. Persistence of the perturbation, however, will lead to further up-regulation. In a study of denervation of a single limb, hyperkalemia was observed as early as 4 days after injury, but the potassium levels did not reach lethal levels, probably related to the duration and limited (single limb) nature of the denervation.[69] The concomitant presence of a pathologic state (*e.g.*, meningitis, head injury) together with immobilization has been reported to cause hyperkalemic cardiac arrest as early as 5 days.[15] Use of nondepolarizing muscle relaxants, clostridial infections, major burns, and quadriplegia are conditions involving many muscle fibers. These pathologic states associated with immobilization may be sufficient to up-regulate receptors to critical levels to cause hyperkalemia even earlier. Therefore, it may seem wise to avoid the use of succinylcholine beyond 48–72 h of denervation/immobilization or any other pathologic state where AChRs are known to increase.[70] Whether severe infection alone, in the absence of confinement in bed, is a contraindication to succinylcholine, is unknown. It should be noted, however, that hyperkalemia to succinylcholine has not been reported in patients with acquired pathologic states of less than 4 days' duration.

The up-regulation of AChRs can persist as long as the condition that induced it continues to be present. Quadriplegics and paraplegics with persistent paralysis, therefore, could have the potential for succinylcholine hyperkalemia throughout life. Succinylcholine hyperkalemia has been seen 8 weeks after recovery from a transient stroke.[71] Hence, the hyperkalemic response to succinylcholine after even transient stroke or denervation may last even after recovery of muscle power. In another patient, cardiac arrest after succinylcholine administration was seen weeks after mobilization and "resolution" of Guillain-Barré syndrome.[72] A pathologic state causing direct damage or inflammation to muscle (*e.g.*, radiation to muscles, or metastatic rhabdomyosarcoma) may cause sufficient up-regulation of AChRs to cause hyperkalemia after succinylcholine.[73,74] Rhabdomyosarcoma is a muscle tumor expressing high quantities of AChRs. Compared with simple immobilization, the use of muscle relaxants will cause more profound increases in AChRs.[26,75] It is also unknown, however, when this AChR up-regulation, in critically ill intensive care unit patients who have had critical illness neuropathy/myopathy and/or muscle relaxants, reverts to normal. The recovery of muscle dysfunction can be delayed as long as 1–5 yr after critical illness and prolonged stay in the intensive care unit.[76,77] The relation of this muscle dysfunction to AChR number is unclear. Therefore, it seems prudent to avoid succinylcholine in patients who have recovered recently from critical illness, particularly if muscle function is still abnormal. Our experience with burned patients suggests that AChRs return to normal levels when wounds are healed, protein catabolism has subsided, and the patient is mobile. This healing process may

take well over 1–2 yr after wound coverage in patients with major (80% body surface area) burns. If immobilization persists as a result of severe contractures or other reasons, the up-regulation will not be abated. We have observed resistance to nondepolarizers as long as 1 yr after complete healing of a 35% body surface area burn and discharge from the hospital.[78] This would suggest that the chance for hyperkalemia may still be present, although the potassium levels may or may not reach lethal levels at this late stage.

Conclusion

With US Food and Drug Administration approval of the fast onset nondepolarizing relaxant, rapacuronium, the use of succinylcholine was expected to dwindle.[79] With the removal of rapacuronium from the market because of its severe bronchoconstrictive effects, the use of succinylcholine has continued in the hospital and even outside the hospital setting, particularly when there is a need for rapid onset and offset of effect.[3–11] A lethal hyperkalemic response can result in certain susceptible individuals. Immobilization of skeletal muscle, whether anatomically, chemically, physically, pathologically, or iatrogenically induced, results in up-regulation of AChRs at the muscle membrane. Inflammation, damage of muscle, or both, as seen in burn injury, radiation injury, or tumor, can also cause profound up-regulation of AChRs.[10,46,48,73,74]

The up-regulated AChRs consist of the well-studied conventional muscle AChRs with a subunit composition of $2\alpha1$, $\beta1$, δ, and ε/γ subunits and the recently identified neuronal $\alpha7$AChRs in muscle. Systemically administered succinylcholine has the potential to depolarize all AChRs throughout the muscle membrane. The extrajunctional immature AChRs are depolarized more easily with succinyl choline and release potassium for prolonged periods. The $\alpha7$AChRs can also be depolarized by succinylcholine as well as its metabolite, choline.[18] Because the $\alpha7$AChR channels desensitize less easily, the potential for a greater and continued release of potassium due to depolarization by succinylcholine and choline exists and may account for the persistence of hyperkalemia even after the effect of succinylcholine on muscle paralysis has worn off. The clinical importance of $\alpha7$AChRs in the hyperkalemic response to succinylcholine needs further study. The hyperkalemic response to succinylcholine is directly proportional to the up-regulation of AChRs (fig. 5). The potential for severe hyperkalemia with succinylcholine can occur as early as 4–5 days of immobilization/denervation, particularly in association with another pathologic state which in and of itself can up-regulate AChRs. It therefore seems prudent to avoid succinylcholine 48–72 h after "denervation states." Nondepolarizing muscle relaxants can block neuronal $\alpha7$AChRs and conventional AChRs in muscle, but much higher doses are required, and pretreatment with nondepolarizing relaxants in the usual doses will not prevent succinylcholine-induced hyperkalemia.[9] In conditions where AChRs are increased, even a high dose of a nondepolarizing relaxant (e.g., 1.2 mg/kg rocuronium) does not have an onset time comparable to that of succinylcholine.[80]

The purpose of this review is to emphasize that individual pathologic states enumerated in table 1 can lead to up-regulation of AChRs with a potential for hyperkalemia with succinylcholine. The presence of two or more etiologic factors will magnify the up-regulation of AChRs in muscle, which in turn can lead to earlier and more profound hyperkalemic response to succinylcholine.[25–28] It is important to note that, even in the absence of denervation states, hyperkalemia and cardiac arrest can occur in certain conditions after the administration of succinylcholine. Some of these conditions include certain congenital muscle dystrophies[8] and exsanguinating hemorrhage with acidosis.[81,82] The underlying mechanisms for this hyperkalemic response in these situations, where no up-regulation of AChRs has been reported, are unclear.

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