# PERIODIC PARALYSIS

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February 29, 1996

# INTRODUCTION

The periodic paralyses comprise a group of disorders of muscle function characterized by episodic (rather than periodic) bouts of weakness. The majority of the forms of familial periodic paralysis are inherited in an autosomal dominant mode, but occasional, sporadic forms of these disorders have also been noted. Classically, these syndromes have been categorized into hypokalemic, normokalemic, and hyperkalemic forms, indicative of the fact that episodes of paralysis in these patients are often associated with changes in the plasma concentration of potassium. In addition, classification schemes of the periodic paralysis have been utilized which distinguish between the primary (hereditary) forms of this disorder, and those forms which are secondary to other conditions, such as hyperthyroidism, as shown in Table I. While these categorizations have been useful for diagnosis and treatment of these disorders, advances in our understanding of the pathophysiologic events underlying these diseases now allow for a definition at a true molecular level. Recent studies have demonstrated that specific mutations in channels participating in muscle contraction account for these diseases. In addition, complementary electrophysiologic analyses have begun to relate these mutations to the observed changes in plasma potassium that have served as the signatures of these disorders. In this protocol, the various forms of familial periodic paralyses are reviewed, and their functional pathology is discussed in the context of the molecular mechanisms responsible for muscle contraction.

Table I
THE PERIODIC PARALYSES

**Hereditary**

Hyperkalemic periodic paralysis
Variants with and without myotonia

Paramyotonia congenita

Hypokalemic periodic paralysis

**Acquired**

Thyrotoxic periodic paralysis
Barium intoxication
Hypokalemia

## GENERAL CLINICAL FEATURES OF THE PERIODIC PARALYSES

**Despite established differences in the precipitating factors and molecular pathologies of the periodic paralyses, the various forms of the disorder share common features in the clinical picture of the paralytic attack. As will be discussed later, these similarities in clinical findings owe to a final pathology that all the forms of the disease share: namely the inexcitability of the muscle fiber itself. Attacks of paralysis can last from minutes to days, and can vary from a mild, localized weakness, to a generalized paralysis. Muscle strength and reflexes are reduced or absent during attacks. Cranial and respiratory muscles are usually spared, but they too can become involved with time, leading to respiratory arrest. Initially, the episodic attacks of paralysis are fully reversible. Subsequently (years after the disease onset), individuals are left with weakness of affected muscle groups between acute attacks. Finally, episodic paralysis can be triggered in afflicted individuals by rest following work, and/or exposure to cold (Caldwell, Engle,**

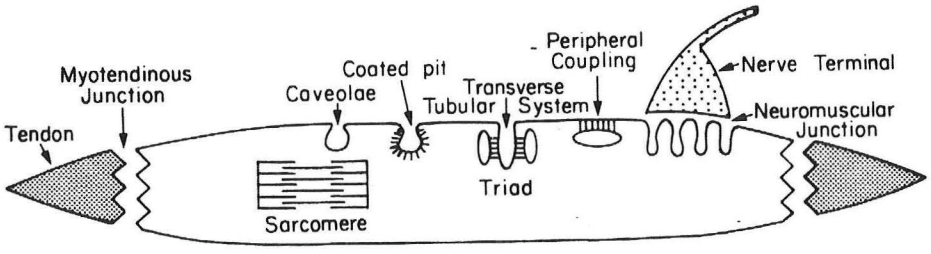
Ptacek, 1994).

Familial forms of hypo-, and hyperkalemic periodic paralysis have recently been demonstrated to result from mutations in ion channels responsible for initiating muscle contraction (Hudson). Discussion of these defects requires an understanding of the general processes involved in muscle contraction, as well as the structure and regulation of ion channels. These topics are briefly reviewed below.

## PHYSIOLOGIC BASIS OF MUSCLE CONTRACTION

The events responsible for the voluntary contraction of skeletal muscle are extraordinarily complex, and involve central signal generation, axonal propagation of the action potential, neuromuscular transmission, and the coupling of the electrical excitation of the myocyte plasma membrane to the final event, physical contraction effected by the machinery of the muscle fiber (Figure 1). For the purpose of this discussion, however, only a general review of the excitation-contraction coupling events is sufficient to allow for discussion of the pathophysiology of the periodic paralysis.

**Fig. 1 SCHEMATIC DRAWING OF A SKELETAL MUSCLE FIBER**



Neuromuscular transmission entails the relay of the neuronal action potential to the surface membrane of the muscle cell, the sarcolemma. This begins with neurotransmitter release from the presynaptic neuron, and the neurotransmitter (acetylcholine) then crosses the cleft to bind to the acetylcholine receptor (Hille) This receptor is in fact a sodium channel itself, but is not involved in the pathology of the periodic paralysis. (It is, however, the target of inhibitory antibodies in myasthenia gravis.) Once acetylcholine binds to this receptor, the channel, or pore, opens, allowing sodium to rush into the muscle cell. This inward movement of positively charged sodium ions diminishes the charge gradient across the membrane, causing depolarization (Figure 2).

In order for muscle contraction to occur in a coordinated fashion, it is essential that the depolarization be simultaneously propagated throughout the myocyte. This requires that sarcomeres internal to the ultimate muscle surface be excited at the same time as the surface fibers. The distance between the surface and internal portion of the muscle is too great for this to be achieved by the simple diffusion of ions. Instead, coordinated propagation is achieved by the transverse, or T tubule system, that serves as a wiring network that directly relays the surface action potential to internal fibers. Topographically, these tortuous invaginations of the plasma membrane penetrate deeply into the cell to allow for the plasma membrane, and extracellular space, to lie in proximity to the inner recesses of the myocyte (Figure 3).

**Fig. 2 ELECTRICAL EVENTS IN THE MUSCLE CELL MEMBRANE OF THE NEUROMUSCULAR JUNCTION.**

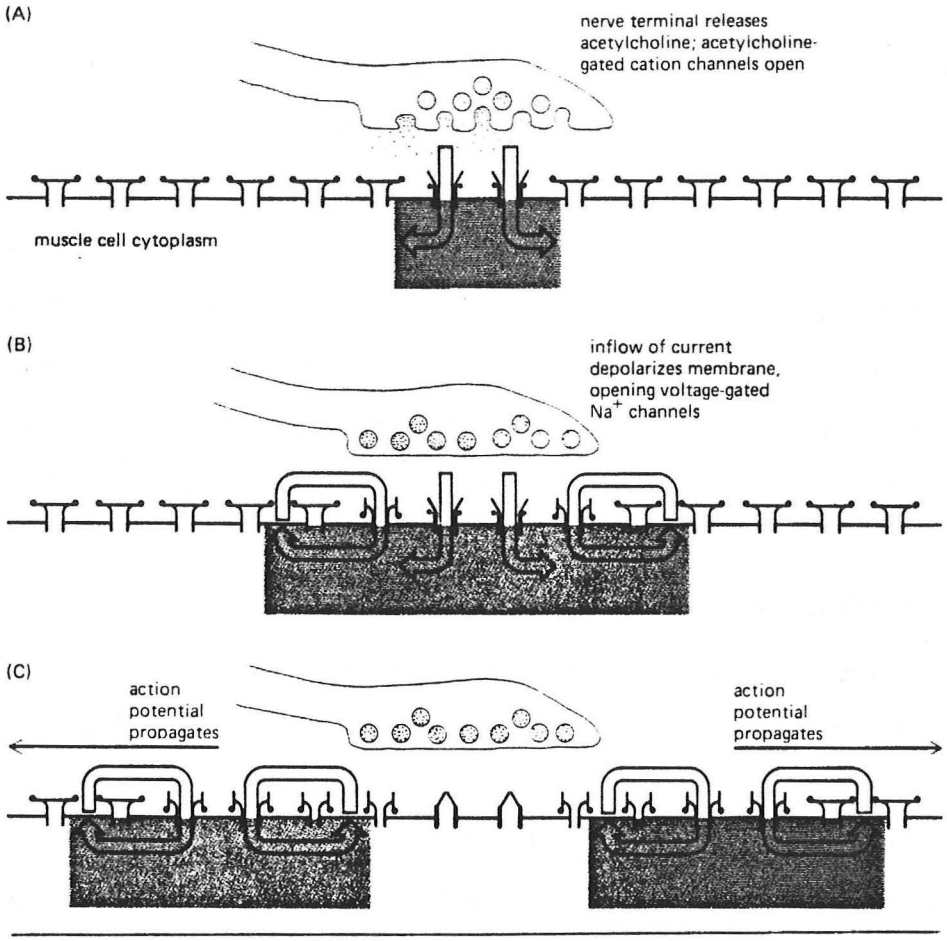
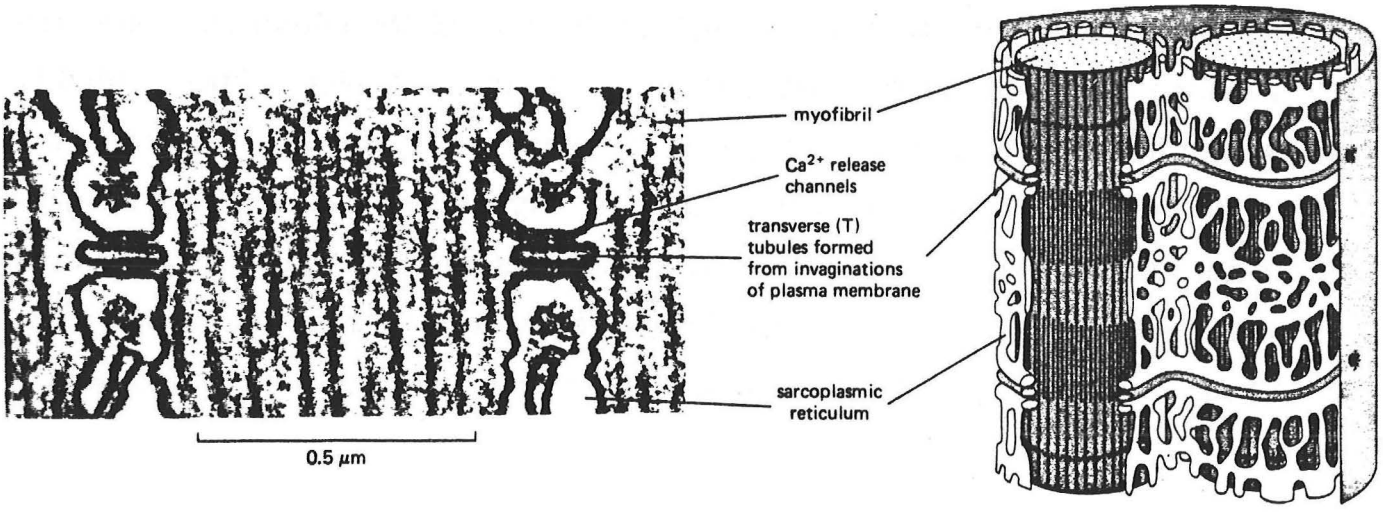



**Fig. 3 T-TUBULE SYSTEM.**

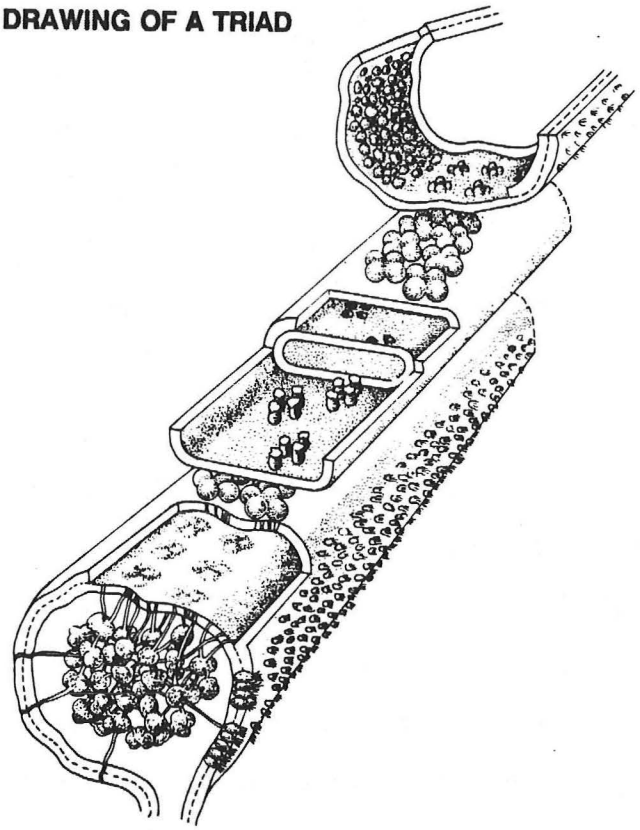


Actual propagation of the action potential is achieved by the sequential opening and closing of ion channels along the surface of the muscle cell and the T-tubules (Engle). Subsequently, the wave of depolarization initiated at the neuromuscular junction is sensed by a voltage-sensitive sodium channel (Barchi). (As will be discussed later, mutations in this channel are responsible for the hyperkalemic form of the periodic paralysis.) With voltage activation, this channel opens to allow for the rapid entry of sodium ions into the myocyte. As a result of this movement of positive charges into the cell, the membrane becomes partially depolarized, and voltage-sensitive potassium channels, also located on the plasma membrane, are triggered to open. Consequently, potassium rapidly exits the cell, during which time the sodium channel deactivates, or closes. In the resulting depolarized state, the cell is relatively rich in sodium and depleted of potassium. Restoration of the normal ionic composition and membrane potential is achieved by the Na+-K+ ATPase, which pumps sodium out of the cell in exchange for potassium.

The surface action potential is generated and propagated by the movement of sodium and potassium, but a rapid rise in cellular calcium is ultimately required for activation of the machinery (actin and myosin) responsible for physical contraction. Details of the mechanism whereby the membrane action potential is coupled to the release of calcium from its storehouse, the sarcoplasmic reticulum, are not fully established. Nonetheless, it is clear that this coupling is transmitted through a specialized architectural arrangement, the triad, in which the T-tubule is interposed between two stacks of the intracellular sarcoplasmic reticulum. Such a triad is shown in Figures 3 and 4. At least two proteins of the triad are involved in the signaling process. The first of these, the dihydropyridine receptor (Elbaz, Hogan), is defective in hypokalemic periodic paralysis. This receptor, which has a channel-like structure, senses the depolarization wave and transmits a signal to a calcium channel of the endoplasmic reticulum, the ryanodine receptor. When activated, the

ryanodine receptor allows calcium to exit the sarcoplasmic reticulum and flood the cytosol, thereby initiating the biochemical events required for contraction. To complete the excitation-contraction cycle, cytosolic calcium is pumped back into the sarcoplasmic reticulum by a calcium-translocating ATPase.

Fig. 4 SCHEMATIC DRAWING OF A TRIAD



## CHANNELS: GENERAL AND SPECIFIC

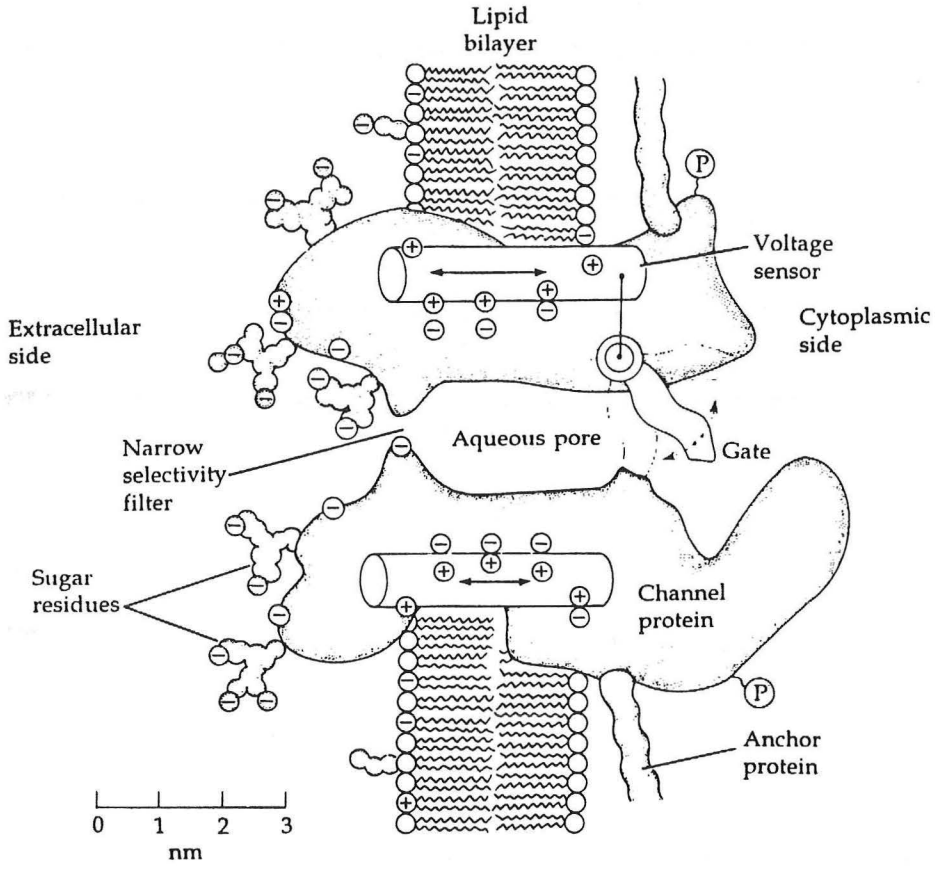
Membrane bilayers are relatively impermeant to most substances, and in particular, to charged molecules and ions. The permeability of the membrane to such species is maintained in a regulated and selective manner by several types of transport proteins, including facilitated transporters (such as the GLUT transporters responsible for glucose transport), ion translocating ATPases (responsible for $H^+$, $Ca^{2+}$, $Na^+$, and $K^+$ movement), and ion channels. Of these transport systems, channels have the greatest "turnover" number, and are capable of facilitating the

flow of more ions per second per single transport protein than any of the other types of transporters. Typically, a single channel, in a strict electrophysiologic sense, can allow for the flow of between $10^6$ and $10^8$ ions per second. Ion channels are thus well suited to the generation and propagation of active potentials in neurons and myocytes, a process that requires rapid, large scale, transmembranous ion flow during the stages of depolarization. Just how ion channels carry out this remarkable feat is not well established; crystallographic analysis is lacking for any ion-selective channel and knowledge of channel structure and function is indirectly based upon biochemical and electrophysiological studies. Shown in Figure 5 is a schematic view of one such channel, the voltage-gated (regulated) sodium channel of skeletal muscle. As shown, this channel is predominantly intramembranous. Central to its function is an interior, aqueous pore through which ions flow, with the net direction of ion movement being governed by charge and chemical gradients across the membrane. Selectivity of ion movement through a channel is obviously important, and this is achieved by a narrow selectivity filter, that only allows for the passage of ions that fall within a very narrow range of size and charge. This portion of the channel is charge-rich, and in this model of a sodium channel, negatively charged amino acids in the vicinity of the selectivity barrier serve to repel negatively charged ions, such as chloride (Hille, Yue).

The other important features of this channel relate to its regulation. It is obviously important that flow through the channel be limited to periods of action potential propagation, and this regulation is achieved by a "gate" portion of the protein. In some channels, this gate has been shown to be a portion of the channel molecule itself, and to be capable of physical movement so as to close or open the entry to the aqueous path (Figure 6).

**Fig. 5 A WORKING HYPOTHESIS FOR THE Na CHANNEL ILLUSTRATING ITS MAIN FUNCTIONAL REGIONS.**

**Voltage-dependent channels must have a charged structure (the voltage sensor)which enables the channel to respond to changes in membrane voltage. Movement of the voltage sensor couples changes in membrane voltage to the opening and closing of the gate, and this charge movement can be recorded as a gating current. The region of the channel referred to as the selectivity filter confers on the channel its specific selectivity for various ions. (Hille)**

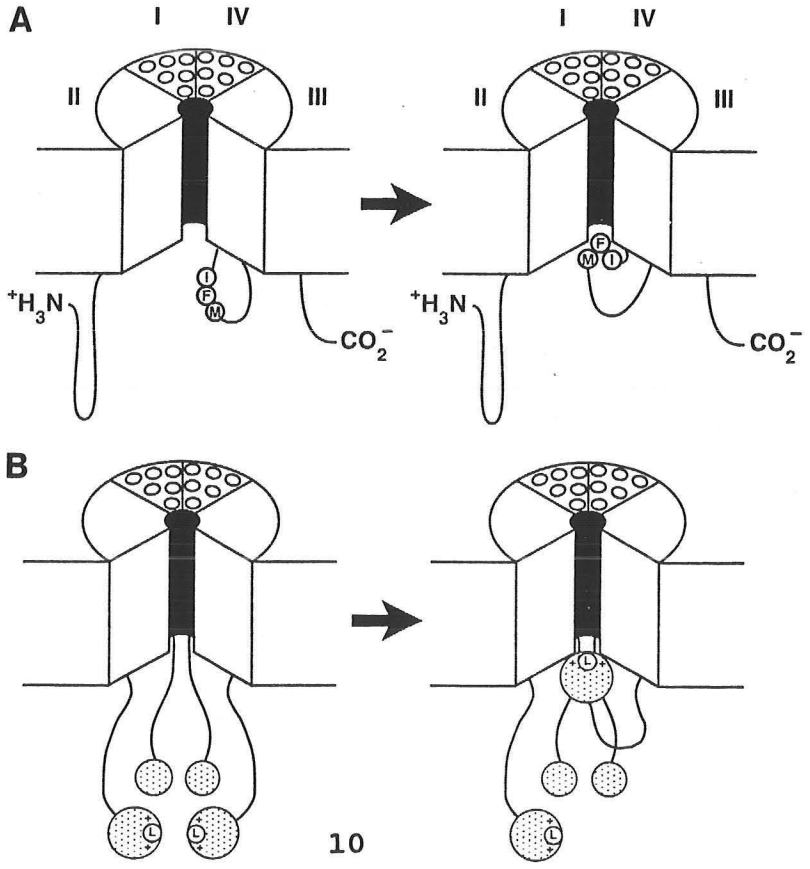



**This opening or closing of the gate is precisely regulated in all channels and its regulation is tuned to the nature of the physiology of the channel system itself. Thus, the opening and closing of some channels is achieved by the binding of**

neurotransmitter molecules, such as acetylcholine, which opens the sodium channel of the neuromuscular junction. Similarly, voltage-gated channels, of the type relevant to the periodic paralyses, open and close in response to voltage changes across the muscle cell plasma membrane. As shown in Figures 5 and 6, voltage sensors are present in the sodium channel of muscle and when this portion of the molecule is exposed to a voltage change, conformational changes occur in this sensor domain, which then lead to an opening of the gate (Barchi, George, Yue).

**Fig. 6 MECHANISMS OF INACTIVATION OF $Na^+$ AND $K^+$ CHANNELS (A) THE HINGED-LID MECHANISM OF $Na^+$ CHANNEL INACTIVATION AND (B) THE BALL-AND-CHAIN MECHANISM OF $K^+$ CHANNEL INACTIVATION.**

**The intracellular loop connecting domains III and IV of the $Na^+$ channel is depicted as forming a hinged lid. The critical residues Leu7 (L7) and Phe1489 (F1489) are shown as occluding the intracellular mouth of the pores in the $K^+$ channel and $Na^+$ channel, respectively. The amino acid sequences of the inactivation particle region of each channel are illustrated at the bottom of the figure, and the open triangle indicates the critical residues in each sequence.**



## HYPERKALEMIC PERIODIC PARALYSIS

Although primary hyperkalemic periodic paralysis shares clinical features with the hypokalemic form of periodic paralysis, it arises from a unique gene defect - that of the skeletal muscle sodium channel. First described in 1951, this disorder was differentiated from the hypokalemic form of periodic paralysis by the mild degrees of hyperkalemia accompanying the attacks. Seldom is the plasma potassium concentration elevated above 5 - 6 meq/l, and thus cardiac abnormalities are uncommon. It is transmitted as an autosomal dominant disorder with complete penetrance in both sexes. Attacks usually are noted in the first decade of life. These are typically brief (15-60 minutes), occur in the morning prior to breakfast, and resolve spontaneously. As with hypokalemic periodic paralysis, rest can provoke attacks, as can cold exposure, emotional stress and pregnancy. In contrast to hypokalemic periodic paralysis, urinary potassium secretion increases during the attacks, likely in response to the hyperkalemia.

Diagnosis is based upon classic paralytic attacks, positive family history, and elevated plasma creatine kinase. In addition, a simple provocative test can be used in which 2-10 grams of KCl is given orally to a fasted patient after exercise. Paralysis typically ensues within 1-2 hours.

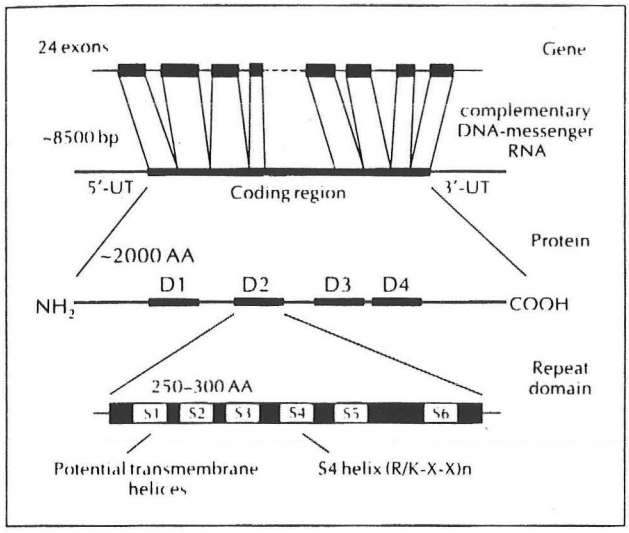
Investigations of the cause of this disorder led to two key observations. First it was found that myocytes from afflicted individuals were extremely sensitive to elevations of extracellular potassium, in that even modest elevations of potassium caused excessive depolarization. Second, it was found that myocyte sodium channels failed to inactivate in the presence of elevated external potassium concentrations. Subsequent genetic analysis revealed tight linkage of hyperkalemic periodic paralysis to the skeletal muscle sodium channel gene on chromosome

17(Koch); later, mutations in this gene were shown to cause the disorder (McClatchey, Ptacek, 1991).

The gene for the α subunit of the voltage-dependent sodium channel of human muscle is depicted in Figure 7. Twenty-four exons are spliced to generate a processed mRNA of about 8500 bp.

**Fig. 7 THE GENE FOR THE α-SUBUNIT OF THE MUSCLE VOLTAGE- DEPENDENT SODIUM CHANNEL CONTAINS 24 EXONS AND IN HUMAN MUSCLE GENERATES A PROCESSED MESSENGER RNA OF APPROXIMATELY 8500 BP.**

**This messenger RNA encodes a protein of approximately 2,000 amino acids (AA). Within its primary structure are four large regions of internal homology (D1-D4), each containing at least six putative transmembrane helices (S1-S6). The fourth helix in each domain contains a characteristic repeating pattern of a positive charge in every third position (arginine [R] lysine [K]) separated by netural amino acids.**




The sodium channel responsible for hyperkalemic forms of periodic paralysis is shown schematically in Figures 8 and 9, where the domains proposed to be responsible for selectivity, gating, and regulation (voltage dependency) are shown.

**Fig. 8 PRIMARY STRUCTURE OF THE α SUBUNIT OF THE SKELETAL MUSCLE SODIUM CHANNEL.**

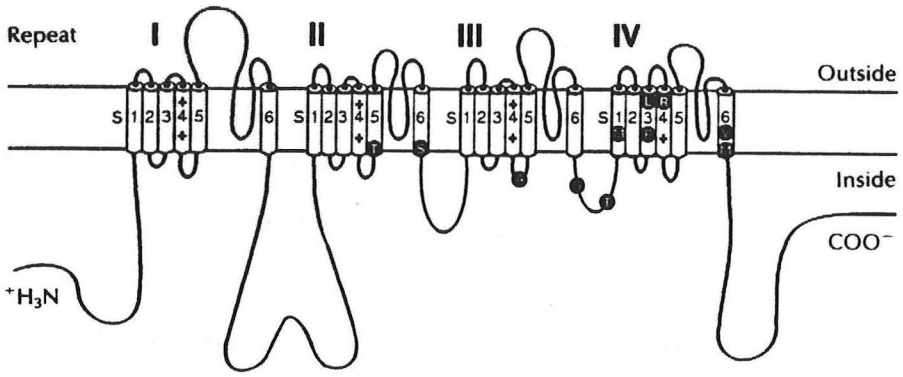
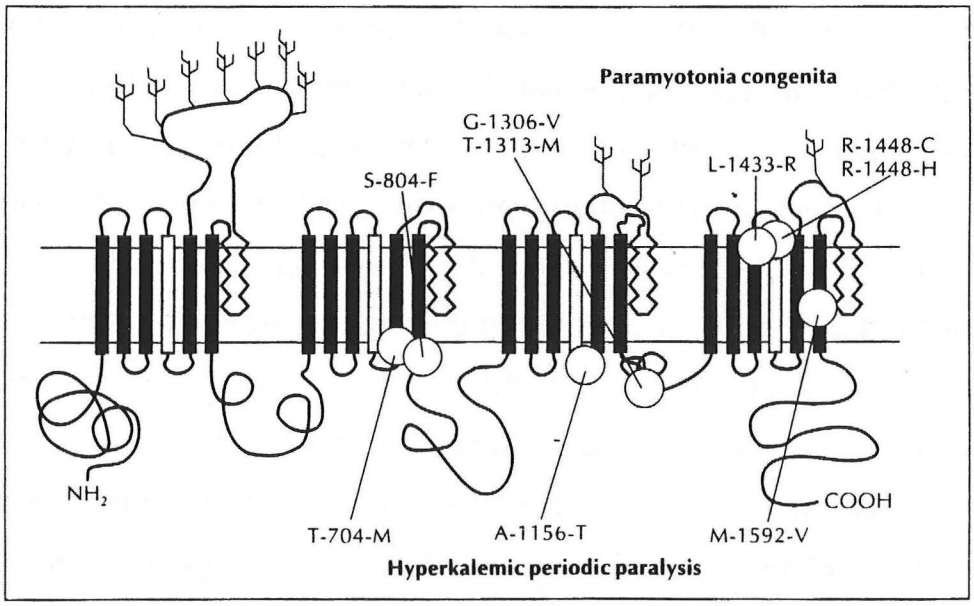



**Fig. 9 MUTATIONS REPORTED IN FAMILIES WITH HYPERKALEMIC PERIODIC PARALYSIS, PARAMYOTONIA CONGENITA, AND OVERLAPPING VARIANTS.**

**Single letter codes for then active amino acid and the mutant substitution are given, separated by a number indicating the position of the mutation in the primary sequence.**



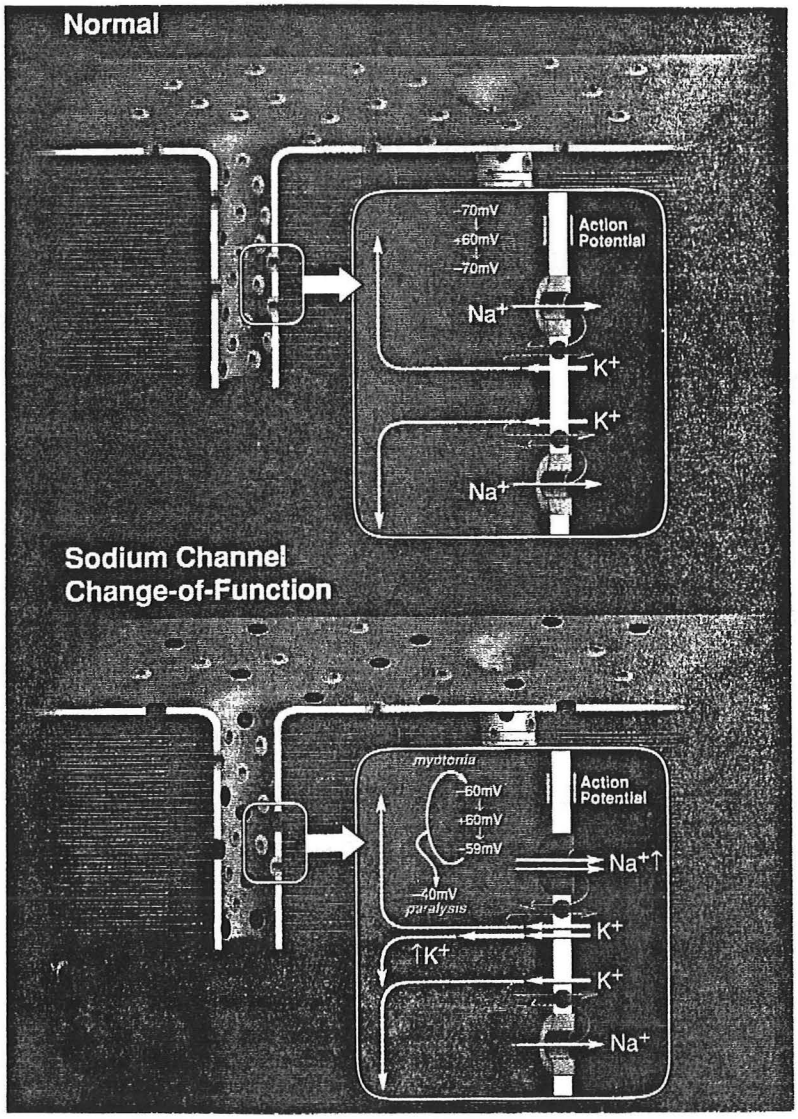
The channel itself is a large, complex hetero-oligomer with an overall molecular mass of over 300 kDa. The $\alpha$ subunit consists of four repeated domains, designated D1-D4, each of which is composed of about 500 amino acids (Barchi, George). There exists about 50% sequence similarity amongst the domains.

Together, these D1-D4 domains are assembled to form the true channel portion of the protein, with each domain forming one quarter of the channel. Each of these domains contains six transmembraneous $\alpha$ helical segments, designated $S_1$-$S_6$. Experimental evidence indicates that the $S_4$ segments of each of the D domains that is responsible for voltage sensing, while the pore is lined by segments between the $S_5$ and $S_6$ helices. The actual gate mechanism has not been identified conclusively, but available evidence implicates the cytoplasmic loop between $D_3$ and $D_4$, a region referred to as a hinged lid.

Depolarization of the sodium channel leads to the functional pathology of this disease by a rather convoluted mechanism. Essentially, the pathophysiologic state of predisposition to weakness owes to the net interplay of normal and mutant sodium channels. As such, hyperkalemic periodic paralysis is typical of many autosomal dominant disorders in which the phenotype is due to a gain (or change) of function rather than a loss of function. This is in contrast to a typical autosomal recessive disorder where the phenotype owes to a loss in the activity of an enzyme, such as in phenylketonuria. Instead gain of function mutations result from persistent but altered activity of the mutant gene product (Hoffman). Figure 10 illustrates the mechanism by which the mutated sodium channel causes hyperkalemic periodic paralysis. Essentially, it does so by being constitutively open such that there is a constant sodium entry pathway on the surface of the T-tubule of skeletal myocytes. Because of this, the muscle cells have a lower (more depolarized) resting membrane potential than normal.

**Fig. 10 HYPOTHETICAL CONSEQUENCES OF SODIUM CHANNEL CHANGE-OF-FUNCTION MUTATIONS ON MEMBRANE POTENTIAL IN HYPERKALEMIC PERIODIC PARALYSIS (HYPERPP) AND PARAMYOTONIA CONGENITA (PC).**

**Shown are representations of muscle membranes and contiguous t-tubules of normal muscle (top) and HyperPP/PC muscle tissues (bottom). Sodium channels, which sense and perpetuate action potentials are distributed in both the plasma membrane and t-tubules of normal muscle. Patients with HyperPP or PC (lower panel) have dominantly inherited change-of-function mutations of one of their sodium channel genes, and therefore, have both normal and abnormal sodium channels in the same fiber. During an action potential in normal muscle (expanded region, top), sodium channels synchronously activate and then quickly inactivate, producing the characteristic series of membrane potential changes at the membrane surface. The transient sodium ion influx causes a reciprocal potassium ion efflux into the lumen of the t-tubules. After the action potential, the sodium and potassium are actively transported by the sodium-potassium adenosine triphosphatase to reestablish a concentration gradient with three sodium ions transported for every two potassium ions. Excess potassium ions that accumulate in the t-tubule lumen diffuse toward the extracellular space. In HyperPP and PC (lower panel), both normal and abnormal sodium channels are present in the myofiber membranes. During an action potential (expanded region, bottom) or at rest (not shown), some mutant sodium channels inactivate less efficiently than normal leading to a persistent inward sodium current. The excess sodium influx prompts a reciprocal potassium efflux into the lumen of the t-tubule. This is thought to lead to an increase in potassium concentration in the t-tubules, which results in a drop in the membrane potential. A number of factors then determine if the membrane potential reaches the threshold for myotonia or the threshold for paralysis. These factors can include the percentage of inactivating mutant channels, the systemic potassium concentrations, the effect of cold on membrane and channel function, the function of the sodium-potassium ATPase and the efficiency of diffusion from the lumen of the t-tubules.**



It is most important is realize that the primary defect in hyperkalemic (and hypokalemic) periodic paralysis do not owe to intrinsic failures of the body as a whole to absorb or secrete potassium. Rather, the distribution of potassium is altered in these patients, and total body potassium content, though usually normal, may be high, or low in during an acute attack. Thus, the treatment of this disorder with potassium-wasting diuretics is not aimed at correcting a whole body potassium surplus. Rather, therapy is aimed at correcting a disorder of potassium distribution that derives from a polarization defect in skeletal muscles, with the goal of achieving a new steady state, in which the plasma potassium concentration is manipulated, relative to myocyte potassium concentration, to achieve a more normal resting membrane potential.

Preventive measures include carbohydrate-rich meals (which drives potassium into cells in an insulin dependent manner) and avoidance of hyperkalemia by means of a low potassium diet; often attacks can be aborted by ingestion of a high carbohydrate load. Acetazolamide has been often used as a potassium-wasting diuretic, largely because of its utility (by another mechanism) in hypokalemic periodic paralyses. Thiazide diuretics are now more commonly prescribed. Finally, mexilitine is of proven benefit in managing severe cases refractory to diet and diuretics (Engle).

## PARAMYOTONICA CONGENITA

This disorder, although not a simple periodic paralysis in the strict sense, is included in this discussion because it is a primary skeletal muscle defect owing to a mutation in the same sodium channel responsible for classic hyperkalemic periodic paralysis (Ebers, Ptacek, Yang). The clinical hallmarks are paradoxical myotonia (myotonia developing during exercise that is aggravated by continued

work), cold aggravation of the myotonia, and predilection for facial, neck and distal upper extremity involvement. In some families, episodes of periodic spontaneous weakness, like those of hyperkalemic periodic paralysis, also occur. In addition to these features, the clinical symptoms of PC differ from those of the classical periodic paralyses, in that the signs of paramyotonia are often present at birth. Cooling of the face produces a mask-like, stiff appearance and in severe attacks the eyes cannot be opened. Also, exposure to cold causes a stiffness in the fingers leading to weakness and ultimately to short-term paralysis. Unlike the classic periodic paralyses, upper extremities are more affected then lower body musculature, and respiratory arrests have not been reported. In addition, neither muscle hypertrophy or atrophy occur with this disorder. The diagnosis is usually based on the presence of a positive family history and clinical signs during infancy, such as transient facial paralysis caused by washing with a cold water cloth. Also, most patents exhibit lid lag. The diagnosis is confirmed by EMG studies, which shows myotonic discharges in all muscle groups. Affected individuals may also have 5- to 10-fold elevations in their plasma levels of CPK, even between attacks.

## EQUINE HYPERKALEMIC PERIODIC PARALYSIS

An interesting parallel to human forms of hyperkalemic periodic paralysis has now been identified in Quarter Horses (Naylor, 1992). These horses, like their human counterparts, have intermittent episodes of muscle spasm accompanied by an elevated plasma potassium level. As is the case in humans, rest immediately following such an attack results in an aggravation of muscle damage. Because of intensive selection inbreeding, this disease has risen to particular prominence in Quarter Horse lines. Thirty percent of Quarter horses, the most popular equine breed in the United States, can trace their lineage to just four stallions, and all of the Quarter Horses effected by hyperkalemic periodic paralysis have had their

ancestry traced to a single common ancestor (Rudolph, Womack).

At first glance, it is surprising that a disorder of muscle function would be found in animals that have been selectively bred since the 1600's to participate in quarter mile races. Reportedly, none of the horses afflicted with this disorder have ever won (placed, or showed) in a race. The reason for the propagation, and indeed expansion, of the mutation within the gene pool of Quarter Horses owes to their appearance of the afflicted animals. Analysis of the records of the show performance of these horses (ie, non-physical competition) reveals that afflicted horses have been disproportionaly rewarded by show judges over their normal peers. The reason for this selective advantage owes to the prized, highly muscular appearance of horses carrying the mutation; 'pronounced muscularity' is a most desired trait according to the American Quarter Horse Association's description of the breed (Naylor,1994). Presumably, the hypertrophy of the horse flesh owes to the 'passive' exercise of the episodic spasm characteristic of the disorder.

Recent characterization of the gene encoding the equine skeletal muscle sodium channel has confirmed what was suggested by electromyelographic studies: that indeed the Quarter Horse form of hyperkalemic periodic paralysis owes to a mutation in the transport protein and specifically to a domain that accounts for many of the human mutations (Rudolph, Cannon,1995).

Most of the dysfunction attributable to hyperkalemic periodic paralysis in Quarter Horses does not become manifest until the training years, again doing little to hurt sale of the afflicted ponies. Two horses have been found that are homozygous for the $Na^+$ channel mutation. One such horse, which was noted to be particularly well-developed, "had an audible inspiratory noise when restrained." Endoscopic examination demonstrated paralysis of pharyngeal and laryngeal muscles, with

attendant upper respiratory obstruction. In addition, both of these horses developed muscle spasms early in life, suggesting a more severe course; however, homozygosity is obviously not incompatible with life (Naylor).

## FAMILIAL HYPOKALEMIC PERIODIC PARALYSIS

Hypokalemic periodic paralysis, the best known of the hereditary periodic paralyses, was first described in the late nineteenth century. Numerous subsequent case reports, and kindred studies have led to a general clinical view of the disorder. The disease has an autosomal dominant pattern of inheritance and sporadic, or new mutations leading to this disorder are relatively rare. Overall, the disease incidence is 1 in 10,000. The most common precipitants of paralytic episodes are heavy exercise followed by rest, and carbohydrate-rich meals; attacks upon awakening are relatively frequent in the disorder. Males oftentimes have a more severe phenotype then do females, perhaps due to the relationship between heavy exercise and acute attacks. Paradoxically, limited exercise is often protective and can stave off developing attacks (Engle).

The level of muscle weakness can range from mild to frank paralysis and can last from a few minutes to days; occasionally, patients can have week-long bouts of paralysis. Proximal muscles tend to be more severely affected then distal muscles and during a paralytic attack, weakness spreads form proximal to distal muscle groups. Typically, the lower extremities are affected more severely than the upper extremities and involvement of the truncal musculature is common. Because of the latter, patients often can not urinate during an attack; this owes to abdominal musculature weakness and not to any defect in smooth muscle, which is spared in these disorders.

Attacks are commonly self-limited and in general there are no immediate residual deficits. Death is rare, and when it does occur it is caused by paralysis of the laryngeal muscles, or very rarely the diaphragm. This observation has been attributed to the general finding that mild exercise is of prophylactic benefit, and thus the restless diaphragm is spared.

A detailed report of the clinical and laboratory features of a large kindred that included 120 family members spanning five generations has served to provide a unified view of the disease and its manifestations. In this study, the mean age of initial paralytic attacks was 15.6 years of age for men, and 14.9 years of age for women. The average attack rate during the first five years of manifest disease was 19 attacks/year for women, and 14 attacks/year for men. In both sexes, the attack rate generally declined after puberty, becoming decreasingly common by the ages of 30, and rare after the age of 50.

Laboratory evaluation during the attacks revealed that in 22 patients, hypokalemia ranged from 1.2 - 2.3 meq/l. Provocative factors leading to attacks of hypokalemic periodic paralysis included emotional stress, exercise, cold exposure and ingestion of carbohydrates with meals; Chinese food, in particular, was identified as a trigger for paralytic attacks in some of these individuals. Paralytic attacks typically occurred between two and twelve hours after the provocative event. In addition, menstruation was also found to be temporally related to attacks, and more convincingly, pregnancy resulted in an increase in the frequency and severity of attacks (Links).

As noted previously, permanent muscle weakness is one of the most devastating features of all the periodic paralysis, and is evidently unrelated to the number and/or severity of the preceding acute attacks. Indeed, patients who have had no

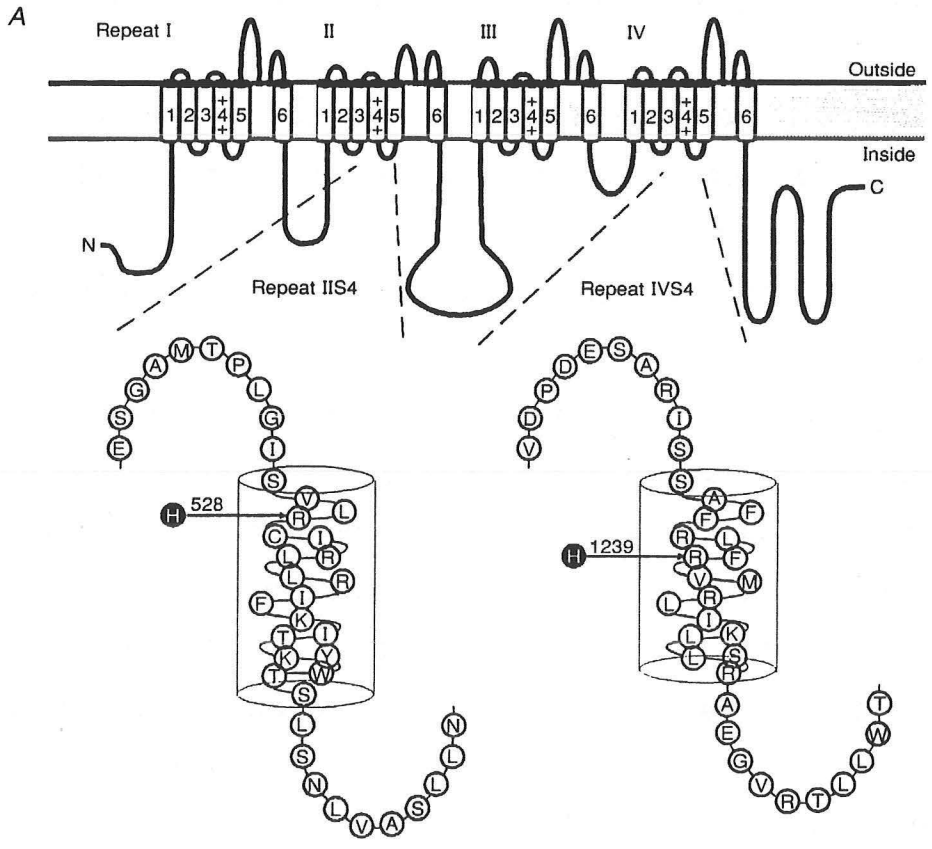
memorable paralytic attacks can be destined to this debilitation. This syndrome of permanent muscle weakness becomes manifest after the age of 40-50 years and is characterized by a weakness of the knees, and pain and stiffness in the back and upper legs. It is not possible to predict which individuals within a kindred are destined to develop this disorder. Biopsy and autopsy specimens from these individuals has revealed the presence of multiple vacuoles, and it has been determined that these represent bloated, degenerated triads; pathology examinations have otherwise been unrevealing as to etiology.

Interestingly, empiric treatment of the disorder with potassium salts was found to be an effective treatment for acute paralytic attacks long before it was discovered in 1934 that the acute episodes of weakness were associated with a fall in the potassium concentration. This observation, though benefiting patients in the first half of the century, misled many investigators as to the etiology of the disorder.

Investigations of the basis for hypokalemic periodic paralysis have unequivocally demonstrated several key points. First, the hypokalemia of this disease is caused by a shift of potassium into muscle, and not by total body potassium deficiency. Second, acute paralytic attacks are due to an inexcitability of the muscle plasma membrane. Third, this refractoriness can be overcome by directly raising intracellular calcium in myocytes harvested from affected individuals, thus indicating that contraction events distal to calcium release from the sarcoplasmic reticulum are intact. Fourth, the resting membrane potential of myocytes is lowered during attacks, that is, the cells are partially depolarized (Fontaine). Because of these observations, suspicions arose that this disease was due to a primary ion transport defect, despite the fact that electrophysiologic studies could not demonstrate any primary dysfunction of the surface sodium and potassium channels of myocytes.

**Recently, a directed genome search within a large kindred led to the finding that hypokalemic periodic paralysis was genetically attributable to point mutations in the dyhydropyridine receptor of the skeletal muscle sarcoplasmic reticulum (Boerman, Elbaz, Sipos). As discussed previously, this protein serves as a critical bridge in the coupling of excitation to skeletal muscle contraction, and directly interacts with the calcium channel (ryanodine receptor) of the sarcoplasmic reticulum. Its structure, shown in Figure 11, resembles that of the skeletal myocyte sodium channel (Figure 8), reflecting a common phylogenetic origin of the two proteins.**

**Fig. 11 MODEL OF MUTATION IN THE $Ca^{2+}$ CHANNEL RESPONSIBLE FOR HYPOKALEMIC PERIODIC PARALYSIS.**



**The two main mutations found in families with hypokalemic periodic paralysis occur in the S4 segments of the protein; these helices constitute part of the putative charge sensing domain of the protein, and it is evident how these mutations might result in a failure to sense an action potential. Despite these findings, explanation of the hypokalemia that accompanies paralytic attacks is not possible at present, although speculations center upon secondary defects in the sarcolemma.**

**Treatment of the hypokalemic form of periodic paralysis entails a combination of drug therapy as well as preventive measures. Mild attacks are often self-terminating, and do not require any treatment. Longer or more severe episodes often respond to treatment with 2 to 10 grams of KCl given orally; response typically occurs in one hour. This dose of KCl can be repeated in 3-4 hours if the recovery is incomplete. Intravenous potassium is generally to be avoided, because of rebound release of potassium from muscle after cessation of the attack with resultant life-threatening hyperkalemia. In addition, acetazolamide can be extremely effective as a preventive measure. Doses range from 125 mg every other day, to 250 mg twice daily. Although it may seem paradoxical to treat hypokalemic periodic paralysis with a diuretic, the hyperchloremic metabolic acidosis that ensues is dominant in terms of benefit. It has been proposed that the mild systemic acidosis caused by acetazolamide results in protons entering cells and, in maintenance of net electroneutrality, potassium is shifted out of cells, somehow serving to ameliorate the ultimate pathology of the disorder: disordered polarization of the muscle cell membrane.**

**In severe cases neither KCl supplementation nor acetazolamide have been fully effective. In such instances, benefit has been achieved by the use of spironolactone or triamterene, both of which are potassium-sparing diuretics that cause a hyperchloremic metabolic acidosis. Also, diazoxide, which inhibits both**

carbonic anhydrase activity and insulin secretion, has been of temporary benefit in preventing paralytic attacks. Finally, verapamil and lithium are promising agents for severe cases, although more clinical trials are required before they can be recommended for general use in this disorder (Confavreux). Other preventive measures are tailored to the individual and his or her idiosyncratic precipitating factors. These include avoidance of strenuous exercise and carbohydrate-rich meals. Sometimes ethanol and caffeine can provoke attacks in susceptible individuals.

## CONCLUSION

Although a clinical picture of a "typical" patient with PP has been derived from large kindred studies, it is important to realize that there can be significant individual variation in the disease phenotype, even within a family. Some individuals carrying the gene for the hypokalemic form may have weekly episodes of paralysis yet others may remain disease free, with their genotype being detected only during kindred screenings. Multiple factors likely account for this variability in expression. First, environmental factors play a major role in provocation of paralytic attacks, as was previously reviewed. These may be inherent to a given individual's lifestyle (e.g. exercise ) or culture (e.g. carbohydrate-rich diet). Second, it is clear that there is both allelic and nonallelic genetic heterogeneity in periodic paralyses. In the hyperkalemic forms of the disorder, pedigrees have been identified in which the disorder is not linked to the sodium channel gene on chromosome 17. In one such family, the phenotype of four afflicted individuals differs from the typical pattern observed in HPP in that paralytic attacks occur during the first year of life. In these individuals, heat, rather than cold, is a reproducible trigger for episodic paralysis (Plassart). Another form of periodic paralysis, Andersen's Syndrome is likewise not linked to the sodium channel gene (Tawil). Although these patients suffer from typical potassium-sensitive paralytic episodes, they also have cardiac dysrythmias that can be fatal (Basquero). Also, these patients have dysmorphic features of the

face and hands which are not seen with the more common forms of periodic paralyses. Third, it is highly likely that there is allelic variation in the gene encoding the common form of hyperkalemic periodic paralysis and that this results in a variable phenotype. Although too few kindreds have been clinically and molecularly characterized to allow for definitive linkage of a phenotype to a specific mutation of the sodium channel (Feero), the fact that mutations within the same gene can lead to either classic hyperkalemic periodic paralysis or paramyotonia congenita is sound evidence for this origin of variability in phenotype.

Lastly, recent studies have suggested that phenotypic variability may derive from differences in the ratio of normal to mutant sodium channels in skeletal muscles. This has been examined indirectly by quantitative analysis of the mRNA levels encoding the normal and mutant sodium channel in Quarter Horses. Analysis of Quarter Horses allowed for the study of a kindred including some 50,000 horses whose ancestry was of greater certainty then would every be possible in a human study. A higher normal/mutant mRNA level was found in horses with no disease than in animals with paralytic attacks of moderate severity. Given the delicacy of the balance leading to resting membrane potentials in this disorder, minor changes in the ratio of normal to mutant channels can easily account for major physiological changes. Future studies are required to determine whether these changes in mRNA levels are truly reflected in protein expression (Zhou).

Molecular definition of the causes of the periodic paralyses promises to allow for classification, diagnosis and treatment of these disorders as well-defined "channelopathies," instead of the symptom and sign based approach of the past. Obvious gaps in our understanding of these diseases remain; in particular, the relationship of the dysfunction of specific channels to local and systemic changes in potassium concentrations.

## REFERENCES


Baquero, J.L., Ayala, R.A., Wang, J., Curless, R.G., Ferro, W.G. Hoffman, E.P., and Ebeid, M.R. Hyperkalemic periodic paralysis with cardiac dysrhythmia: a novel sodium channel mutation? *Annals of Neurology* 37:408-411, 1995.

Barchi, R.L. Ion channels and disorders of excitation in skeletal muscle. *Current Opinion in Neurology & Neurosurgery* 6:40-47, 1993.

Boerman, R.H., Ophoff, R.A., Links, T.P., van Eijk, R., Sandkuijl, L.A., Elbaz, A., Vale-Santos, J.E., Wintzen, A.R., van Deutekom, J.C., Isles, D.E., and et al. Mutation in DHP receptor alpha 1 subunit (CACLN1A3) gene in a Dutch family with hypokalaemic periodic paralysis. *J. of Medical Genetics* 32:44-47, 1995.

Caldwell, J.H., and Schaller, K.L. Opening the gates on ion channel diseases. *Nature Genetics* 2:87-89, 1992.

Cannon, S.C., Brown Jr., R.H. and Corey, D.P. A sodium channel defect in hyperkalemic periodic paralysis: potassium-induced failure of inactivation. *Neuron* 6:619-626, 1991.

Cannon, S.C., and Strittmatter, S.M. Functional expression of sodium channel mutations identified in families with periodic paralysis. *Neuron* 10:317-326, 1993.

Cannon, S.C., and Corey, D.P. Loss of $Na^+$ channel inactivation by anemone toxin (ATX II) mimics the myotonic state in hyperkalaemic periodic paralysis. *J. of Physiology* 466:501-520, 1993.

Cannon, S.C., Hayward, L.J., Beech, J., and Brown, Jr., R.H. Sodium channel inactivation is impaired in equine hyperkalemic periodic paralysis. *J. of Neurophysiology* 73:1892-1899, 1995.

Casley, W.L., Allon, M., Cousin, H.K., Ting, S.S., Crackower, M.A., Hashimoto, L., Cornelis, F., Beckmann, J.S., Hudson, A.J., and Ebers, G.C. Exclusion of linkage between hypokalemic periodic paralysis (HOKPP) and the candidate loci. *Genomics* 14:492-494, 1992.

Confavreux, C., Garassus, P., Vighetto, A., and Aimard, G. Familial hypokalemic periodic paralysis: prevention of paralytic attacks with lithium gluconate. *J. of Neurology, Neurosurgery & Psychiatry* 54:87-88, 1991.

Ebers, G.C., George, A.L., Barchi, R.L., Ting-Passador, S.S., Kallen, R.G., Lathrop, G.M., Beckmann, J.S., Hahn, A.F., Brown, W.F., Campbell, R.D., and et al. Paramyotonia congenita and hyperkalemic periodic paralysis are linked to the adult muscle sodium channel gene. *Annals of Neurology* 30:810-816, 1991.

Elbaz, A., Vale-Santos, J., Jurkat-Rott, K., Lapie, P., Ophoff, R.A., Bady, B., Links, T.P., Piussan, C., Vila, A., Monnier, N., et al. Hypokalemic periodic paralysis and the dihydropyridine receptor (CACNL1A3): genotype/phenotype correlations for two predominant mutations and evidence for the absence of a founder effect in 16 Caucasian families. *American J. of Human Genetics* 56:374-380, 1995.

Engle, A.G. "Periodic Paralysis" in Myology, 2nd. Ed. A.G. Engle and C. Franzini-Armstrong (eds) New York, McGraw Hill, vol 2,1994.

Feero, W.G., Wang, J., Barany, F., Zhou, J., Todorovic, S.M., Conwit, R., Galloway, G., Hausmanowa-Petrusewicz, I., Fidzianska, A., Arahata, K., and et al. Hyperkalemic periodic paralysis: rapid molecular diagnosis and relationships of genotype to phenotype in 12 families. *Neurology* 43:668-673, 1993.

Fontaine, B. Periodic paralysis and voltage-gated ion channels. *Kidney Int.* 49:9-18, 1996

Fontaine, B. Primary periodic paralysis and muscle sodium channel. *Advances in Nephrology* 23:191-197, 1994.

George, Jr., A.L., Komisarof, J., Kallen, R.G., and Barchi, R.L. Primary structure of the adult human skeletal muscle voltage-dependent sodium channel. *Annal of Neurology* 31:131-137, 1992.

Hille, B. *Ionic Channels of Excitable Membranes,* 2nd Ed Sunderland, Massachusetts, Sinauer, 1992.

Hoffman, E.P. and Wang, J. Duchenne-Becker muscular dystrophy and the nondystrophic myotonias. Paradigms for loss of function and change of function of gene products. *Archives of Neurology* 50:1227-1237, 1993.

Hogan, K., Powers, P.A., and Gregg, R.G. Cloning of the human skeletal muscle alpha 1 subunit of the dihydropyridine-sensitive L-type calcium channel. *Genomics* 24:608-609, 1994.

Hudson, A.J., Ebers, G.C., and Bulman, D.E. The skeletal muscle sodium and chloride channel diseases. *Brain* 118:547-563, 1995.

Kantola, I.M. and Tarssanen, L.T. Familial hypokalemic periodic paralysis in Finland. *J. of Neurology, Neurosurgery & Psychiatry* 55:322-324, 1992.

Koch, M.C., Ricker, K., Otto, M., Grimm, T., Hoffman, E.P., Rudel, R., Bender, K., Zoll, B., Harper, P.S., and Lehmann-Horn, F. Confirmation of linkage of hyperkalemic periodic

paralysis to chromosome 17. *J. of Medical Genetics* 28:583-586, 1991.

Lehmann-Horn, F., Iaizzo, P.A., Hatt, H., and Franke, C. Altered gating and conductance of $Na^+$ channels in hyperkalemic periodic paralysis. *Pflugers Archiv - European J. of Physiology* 418:297-299, 1991.

Links, T.P., Smith, A.J., Oosterhuis, H.J., and Reitsma, W.D. Potassium channels in hypokalemic periodic paralysis: a key to pathogenesis? *Clinical Science* 85:319-325, 1993.

Links, T.P., Smit, A.J., Molenaar, W.M., Zwarts, M.J., and Oosterhuis, H.J. Familial hypokalemic periodic paralysis. Clinical, diagnostic and therapeutic aspects. *J. of the Neurological Sciences* 122:33-43, 1994.

Links, T.P., van der Hoeven, J.H., and Zwarts, M.J. Surface EMG and muscle fibre conduction during attacks of hypokalemic periodic paralysis. *J. of Neurology, Neurosurgery & Psychiatry* 57:632-634, 1994.

McClatchey, A.I., McKenna-Yasek, D., Cros, D, Worthen, H.G., Kuncl, R.W., DeSilva, S.M., Cornblath, D.R., Gusella, J.R., and Brown, Jr., R.H. Novel mutations in families with unusual and variable disorders of the skeletal muscle sodium channel. *Nature Genetics* 2:148-152, 1992.

Naylor, J.M, Robinson, J.A., Crichlow, E.C., and Steiss, J.E. Inheritance of myotonic discharges in American quarter horses and the relationship to hyperkalemic periodic paralysis. *Canadian J. of Veterinary Research* 56:62-66, 1992.

Naylor, J.M. Selection of quarter horses affected with hyperkalemic periodic paralysis by show judges. *J. of American Veterinary Medical Association* 204:926-928, 1994.

Pickar, J.G., Spier, S.J., Harrold, D., and Carlsen, R.C. [3H] ouabain binding skeletal muscle from horses with hyperkalemic periodic paralysis. *American J. of Veterinary Research* 54:783-787, 1993.

Plassart, E., Reboul, J., Rime, C.S., Recan, D., Millasseau, P., Eymard, B., Pelletier, J., Thomas, C., Chapon, F., Desnuelle, C. and et al. Mutations in the muscle sodium channel gene (SCN4A) in 13 French families with hyperkalemic periodic paralysis and paramyotonia congenita: phenotype to genotype correlations and demonstration of the predominance of two mutations. *European J. of Human Genetics* 2:110-124, 1994.

Ptacek, L.J., George Jr., A.L., Griggs, R.C., Tawil, R., Kallen, R.G., Barchi, R.L., Robertson, M., and Leppert, M.F. Identification of a mutation in the gene causing hyperkalemic periodic paralysis. *Cell* 67:1021-1027, 1991.

Ptacek, L.J., Trimmer, J.S., Agnew, W.S., Roberts, J.W., Petajan, J.H., and Leppert, M. Paramyotonia congenita and hyperkalemic periodic paralysis map to the same sodium-channel gene locus. *American J. of Human Genetics* 49:851-854, 1991.

Ptacek, L.J., Tyler, F., Trimmer, J.S., Agnew, W.S., and Leppert, M. Analysis in a large hyperkalemic periodic paralysis pedigree supports tight linkage to a sodium channel locus. *American J. of Human Genetics* 49:378-382, 1991.

Rojas, C.V., Wang, J.Z., Schwartz, L.S., Hoffman, E.P., Powell, B.R., and Brown Jr, R.H. A Met-to-Val mutation in the skeletal muscle $Na^+$ channel alpha-subunit in hyperkalemic periodic paralysis. *Nature* 354:387-389, 1991.

Ptacek, L.J. Ion channel shake-down. *Nature Genetics* 8:111-112, 1994.

Ptacek, L.J.,Tawil, R., Griggs, R.C., Meola, G., McManis, P., Barohn, R.J., Mendell, J.R., Harris, C., Spitzer, R. Santiago, F. and et al. Sodium channel mutations in acetazolamide-responsive myotonia congenita, paramyotonia congenita, and hyperkalemic periodic paralysis. *Neurology* 44:1500-1503, 1994.

Rudolph, J.A., Spier, S.J., Byrns, G., and Hoffman, E.P. Linkage of hyperkalemic periodic paralysis in quarter horses to the horse adult skeletal muscle sodium channel gene. *Animal Genetics* 23:241-250, 1992.

Rudolph, J.A., Spier, S.J., Byrns, G., Rojas, C.V., Bernoco, D., and Hoffman, E.P. Periodic paralysis in quarter horses: a sodium channel mutation disseminated by selective breeding. *Nature Genetics* 2:144-147, 1992.

Sipos, I., Jurkat-Rott, K., Harasztosi, C., Fontaine, B., Kovacs, L., Melzer, W., and Lehmann-Horn, F. Skeletal muscle DHP receptor mutations alter calcium currents in human hypokalemic periodic paralysis myotubes. *J. of Physiology* 483:299-306, 1995.

Stewart, R.H., Bertone, J.J., Yvorchuk-St. Jean, K., Reed, S.M., and Neil Jr, W.H. Possible normokalemic variant of hyperkalemic periodic paralysis in two horses. *J. of the American Veterinary Medical Association* 203:421-424, 1993.

Tawil, R., Ptacek, L.J., Pavlakis, S.G., DeVivo, D.C., Penn, A.S., Ozdemir, C., and Griggs, R.C. Anderson's syndrome: potassium-sensitive periodic paralysis, ventricular ectopy, and dysmorphic features. *Annals of Neurology* 35:326-330, 1994.

Wang, J., Zhou, J., Todorovic, S.M., Feero, W.G., Barany, F., Conwit, R., Hausmanowa-Petrusewicz, I., Fidzianska, A., Arahata, K., Wessel, H.B., and et al. Molecular genetic and genetic correlations in sodium channelopathies: lack of founder effect and evidence for a second gene. *American J. of Human Genetics* 52:1074-1084, 1993.

Womack, J.E. Veterinary medicine. Molecular genetics arrives on the farm. *Nature*

360:108-109, 1992.

Yang, N., Ji, S., Zhou, M., Ptacek, L.J., Barchi, R.L., Horn, R., and George Jr., A.L. Sodium channel mutations in paramyotonia congenita exhibit similar biophysical phenotypes in vitro. *Proceedings of the National Academy of Sciences, USA* 91:12785-12789, 1994.

Yue, D.T. Bridging the gap between anomalous sodium channel molecules and aberrant physiology. *Biophysical J.* 65:13-14, 1993.

Zhou, J., Spier, S.J., Beech, J., and Hoffman, E.P. Pathophysiology of sodium channelopathies: correlation of normal/mutant mRNA ratios with clinical phenotype in dominantly inherited periodic paralysis. *Human Molecular Genetics* 3:1599-1603, 1994.