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Teaching course: ion channelopathies in neurology

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Introduction

In 1990 the molecular basis for a hereditary disorder in humans, hyperkalemic periodic paralysis, was first genetically demonstrated to be impaired ion channel function. Since then over a dozen diseases, now termed as channelopathies, have been described. Most of the disorders affect excitable tissue such as muscle and nerve; however, kidney diseases have also been described. Basic research on structure-function relationships and physiology of excitation has benefited tremendously from the discovery of disease-causing mutations pointing to regions of special significance within the channel proteins.

This course focuses mainly on the clinical and genetic features of neurological disturbances in humans caused by genetic defects in voltage-gated sodium, calcium, potassium, and chloride channels. Disorders of skeletal muscle are by far the most studied and therefore more detailed in this text than the neuronal channelopathies which have been discovered only very recently. Review literature may be found in the attached reference list [1–12].

Skeletal muscle sodium channelopathies

Two dominantly inherited and clinically overlapping sodium channelopathies are hyperkalemic periodic paralysis (HyperPP) and paramyotonia congenita (PC). HyperPP is characterized by episodes of flaccid muscle weakness associated with hyperkalemia with signs of myotonia in the interval between attacks; PC is characterized by a stiffening of the muscles during exercise or exposure to cold which can merge into flaccid weakness which may last several hours even when the muscles are rapidly rewarmed. A third allelic disorder, potassium-aggravated myotonia (PAM) is characterized by severe permanent myotonia or fluctuating muscle stiffness that is most prominent about 20 min after exercise (delayed onset myotonia); the mild form is symptomatically very similar to classical dominant myotonia congenita of Thomsen (see "Skeletal muscle chloride channelopathies," below).

As in most other channelopathies, the clinical symptoms and signs of the three diseases, muscle stiffness and – in two of them – muscle weakness are not present all the time. Rather they are elicited by typical stimuli. A typical trigger for an episode of weakness in HyperPP is rest after a heavy work load; stiffness and weakness in paramyotonia congenita are triggered by muscle exercise during

exposure of the muscles to cold, and ingestion of potassium-rich food may induce muscle stiffness in patients having PAM. All these symptoms disappear spontaneously within a few hours. Nevertheless, the episodes hamper the patient's life considerably, although they may be prevented to a certain extent by suitable behavior and symptomatic treatment with drugs.

Genetic studies of large families performed with an intragenic marker quickly revealed that the diseases are linked to *SCN4A*, the gene encoding the α subunit of the skeletal muscle sodium channel. The sodium channels consisting of the main pore-forming α subunit and an accessory β subunit encoded by various genes, is situated in the sarcolemma, and their openings and closings produce the action potential. The key symptoms of stiffness and weakness are explained by the functional defect found in the channel caused by the 21 missense mutations discovered to date. The underlying pathogenetic mechanism is basically the same in all cases, namely a long-lasting, depolarization of the muscle fiber membrane caused by a leaky channel unable to reach or to remain stable in the refractory state (the inactivated state). Keeping in mind that there are two sodium channel populations. mutant and wild type, the pathogenesis of the diseases may be explained. When the membrane depolarization caused by the mutant channels is mild (5–10 mV) wild-type sodium channels can recover from the inactivated state during an action potential and be reactivated by reopenings of the mutant channels, leading to repetitive firing which is the basis for the involuntary muscle activity that patients experience as muscle stiffness. When the depolarization is strong (20–30 mV) the majority of the intact sodium channels adopt the state of inactivation, rendering the muscle fibers inexcitable, which is the basis of the muscle weakness. Heterologous expression of mutant human sodium channel cDNA and patch clamp studies of the resulting currents confirmed these early results and specified the underlying mechanism: disturbances in channel inactivation meaning that channels do not close properly after having opened, a dysfunction that indeed causes sustained membrane depolarization.

Therapy may also be explained by this model. Local anesthetics and antiarrhythmic drugs of class I, such as mexiletine and lidocaine derivatives, are antimyotonic agents because they predominantly block sodium channels in their inactivated state and lead to the phenomenon called use-dependent block. In contrast to the relief of stiffness and of cold-induced weakness, the spontaneous attacks of weakness typical of HyperPP are not affected by mexiletine because no repetitive action potentials occur that can lead to a use-dependent block. Fortunately, diuretics such as hydrochlorothiazide and acetazolamide can decrease frequency and severity of paralytic episodes by lowering serum potassium and perhaps by shifting the pH to lower values.

Skeletal muscle calcium channelopathies

Although familial HypoPP is the most common form of the periodic paralyses in man, it is still a rare disease, showing a prevalence of only 1:100.000. The major symptoms of dyskalemic periodic paralysis, i.e., episodes of generalized paralysis, may occur less frequently and be on average of longer duration than in hyperkalemic periodic paralysis, but there are many cases in which differential diagnosis requires considerable skill of the physician. Decisive for classification is the level of serum potassium during a paralytic attack, which may fall below 2 mmol/l in HypoPP, whereas in the hyperkalemic form it may rise beyond 4.5 mmol/l. Hypokalemia is thought to be caused by stimulation of the sodium-potassium pump by insulin, which is one physiological mechanism by which potassium ions are transported from the extracellular space into the intracellular compartment. Low external potassium concentration theoretically approaching zero may cause electrical destabilization of the cell membrane because the potassium equilibrium then becomes very negative, and the potassium conductance approaches zero. Even in normal muscle external potassium concentrations less than 1.0 mM cause membrane depolarization, and any increase in external potassium causes normalization and stabilization of the resting potential.

Since the discovery of three causative mutations in the gene encoding the pore-forming α_1 subunit of the voltage-gated dihydropyridine receptor (DHPR) calcium channel, *CACNA1S*, in 1994, no additional mutations have been described. Functional studies have not yet clarified the underlying defect causing the hypokalemia or the paralysis (which has also been shown to be depolarization induced) as no clear differences in the mutant channel compared to the wild type have been detected. It is still unclear which of the two functions mediated by the pentameric DHPR, consisting of five separate subunits, is affected: the calcium channel function (long-term maintenance of intracellular calcium homeostasis) or the function of coupling of sarcolemmal excitation to intracellular calcium release necessary for muscle contraction.

Therapeutically, long-term low-dose intake of carboanhydrase inhibitors is recommended to avoid attacks of weakness in HypoPP. During paralysis phases however, oral potassium administration has proven to relieve symptoms. Again, there is no pathogenetic mechanism to explain therapy; these strategies have all been developed on the basis of observation only.

Another calcium channel disorder, malignant hyperthermia (MH) is an autosomal dominantly transmitted predisposition of clinically inconspicuous individuals to respond with uncontrollable skeletal muscle hypermetabolism upon exposure to volatile anesthetics or depolarizing muscle relaxants. The triggering substances lead to an increase in the concentration of free myoplasmic calcium which is released from the sarcoplasmic reticulum cal-

cium stores via the muscle ryanodine receptor channel. During an MH reaction a massive myoplasmic calcium release is induced, leading to muscle contracture especially of the masseter, generalized rigidity, and heat production. Hypermetabolism associated with the sarcoplasmic calcium elevation upregulates glycogenolysis resulting in excess lactate production, metabolic acidosis, and hyperactivation of the oxidative cycle with increased ATP depletion, high oxygen consumption, and carbon dioxide production with hypoxemia and hypercapnia. Tachycardia may be observed as an early sign. During the course of the crisis, rhabdomyolysis occurs with subsequent creatine kinase elevation, hyperkalemia potentially leading to ventricular fibrillation, and myoglobinuria with the possibility of renal failure. Hyperthermia may be a late sign in some cases. If an episode is survived, normalization of edematous muscle and creatine kinase levels occur within 10–15 days.

In the majority of families there are mutations in the gene encoding the skeletal muscle ryanodine receptor, *RYR1*, a calcium channel which is not voltage dependent on its own but under the control of the voltage-dependent DHPR. To date more than 20 disease-causing point mutations in *RYR1* have been identified in humans, all situated in the intracellular part, the foot, of the protein. The base of the homotetrameric protein, void of mutations until now, is located in the membrane of the muscle calcium store, the sarcoplasmic reticulum, and forms the ion-conducting pore. Functionally, hypersensitivity of *RYR1* to anesthetic triggering agents has been shown to be pathogenetic in functional tests of muscle, isolated native proteins, and heterologously expressed full-length receptors. Therapeutically, during an anesthetic crisis dantrolene, an inhibitor of intracellular calcium release, is very effective and reduces the mortality rate, former at 70%, to 10%.

Allelic to the *RYR1* gene locus of MH is central core disease (CCD), a congenital autosomal dominantly transmitted proximal myopathy associated with MH through histological structural alterations mainly of type 1 fibers. The term derives from central areas along the whole fiber length that contain structured or unstructured myofibrils and lack of mitochondria. Affected individuals show hypotonia upon birth (floppy infant syndrome). Muscle strength usually improves later in life except in rare cases showing progressive muscle weakness. Exercise-induced muscle cramps are often reported. Four *RYR1* mutations have been described to date.

MH is very heterogeneous, with five additional loci now known. Only for one of these loci has a causative gene been identified, *CACNA1S*, and two mutations described underlining the functional link between *RYR1* and the DHPR in excitation contraction coupling. Genetic heterogeneity has also been shown for CCD, but no additional loci have been described.

Skeletal muscle chloride channelopathies

Myotonia, at least in humans, may be due not only to sodium channel mutations as in PAM but also to changes in the chloride channel CLC1, such as in autosomal dominant of Thomsen myotonia. Therefore almost indistinguishable clinical features are evoked by two totally different disease pathogenesis mechanisms: on the one hand, disturbed inactivation of the sodium channel, and, on the other, as is the case for classical myotonia congenita, instability of the membrane resting potential due to defects in the sarcolemmal homodimeric chloride channel.

Congenital myotonia (= muscle tension) may show either dominant (Thomsen myotonia) or recessive (Becker myotonia) modes of transmission, both of which may be caused by mutations in *CLCN1*, the gene encoding the major skeletal muscle chloride channel. The dominant form is very rare, as fewer than ten families have been identified at the molecular level up to date. The recessive form is much more common, estimated to occur at a rate of between 1 : 23 000 and 1 : 50 000. Males seem to be affected predominantly (3 : 1) when considering only the typical clinical features. However, family studies disclose that women are affected at the same frequency, albeit to a much less degree.

Muscle stiffness in both variants is temporary and can affect every skeletal muscle of the body. Myotonic stiffness is most pronounced when a forceful movement is abruptly initiated after the patient has rested for 5–10 min. For instance, after making a hard fist, the patient may not be able to extend the fingers fully for several seconds. Myotonia decreases or vanishes completely when the same movement is repeated several times (warm-up phenomenon), but it always recurs after a few minutes of rest. On rare occasions a sudden, frightening noise may cause instantaneous generalized stiffness. The patient may then fall to the ground and remain rigid and helpless for some seconds or even minutes. Typically myotonic muscles reveal a characteristic pattern on electromyography (EMG), for example, bursts of repetitive action potentials with amplitude and frequency modulation, so-called “dive-bombers” in the EMG loudspeaker.

Pathogenetically, the chloride channel shows loss of function meaning the membrane chloride conductance is drastically reduced. Muscle stiffness is caused by the fact that following voluntary excitation the membranes of individual muscle fibers may continue for some seconds to generate runs of action potentials as the stabilizing effect of the chloride for the after-potential is dysfunctional. The electrical excitement causes continuous muscle contraction (= myotonia).

Many myotonia congenita patients can manage their disease without medication. Should treatment be necessary, myotonic stiffness responds well to drugs that reduce the increased excitability of the cell membrane by interfering with the sodium channels, for example, local anes-

thetics, antifibrillar and antiarrhythmic drugs, and related agents. These drugs suppress myotonic runs by decreasing the number of available sodium channels and have no known effect on chloride channels. Of the many drugs tested that can be administered orally, mexiletine is the drug of choice.

Neuronal sodium channelopathies

Generalized epilepsy with febrile seizures (GEFS) is a recently described epilepsy syndrome comprising febrile seizures with onset in the first year of life, but, unlike the typical febrile convulsions, attacks with fever continue beyond the age of 6 years or afebrile generalized seizures (tonic-clonic, myoclonic, myoclonic-astatic, absence, or atonic seizures) and usually cease by the beginning of puberty. Recently a point mutation in the causative gene, *SCN1B,* encoding the voltage-gated sodium channel accessory subunit (β_1 subunit). The mutation disrupts the putative interaction site between the main α subunit and the β subunit of the neuronal sodium channel creating a defect similar to the effects of the skeletal muscle α subunit causing myotonia mutations (disturbances of inactivation) and could explain brain myotonia (neuronal hyperexcitability, epilepsy, GEFS).

Neuronal potassium channelopathies

Autosomal dominant benign familial neonatal convulsions (BFNC) are characterized by brief and frequent generalized seizures, typically commencing within the first week of life and disappearing spontaneously within a few months. Seizure symptoms include tonic movements, shallow breathing, ocular signs (i.e., staring, blinking, gaze deviations), and automatisms. The EEG shows generalized attenuation followed by slow waves, spikes, and burst suppression that are correlated with symptoms. Interictally patients show normal behavior and develop normal intelligence later in life. Seven mutations have been described in the voltage-sensitive neuronal potassium channel gene *KCNQ2* and one in the related *KCNQ3.* The mutations alter the structure of the ion-conducting pore region and/or the cytoplasmic C-term, both leading to a variety of functional defects that explain lack of repolarization during the action potential normally mediated by increase in membrane potassium conductance. This depolarizing tendency again explains neuronal hyperexcitability (epilepsy).

Episodic ataxia 1 (EA1) is an autosomal dominant human disease characterized by attacks of atactic gait with jerking extremity movements that last for seconds to minutes provoked by motion and exercise. Several missense mutations have been detected in the causative gene, *KCNA1,* which encodes the human homologue of the *Shaker* potassium channel, so-called for a *Drosophila melanogaster* mutant displaying ether-induced shaking of legs (ataxia of the fly). In humans interictal twitching in facial muscles and those of distal extremities may occur, indicating that *KCNA1* is expressed not only in brain tissue but also in peripheral motoneurons. This so-called myokyrmia is asscotiated with rhythmic activity of motor units in the EMG.

Disease pathogenesis may be explained by a reduced repolarizing effect of the potassium channel leading to broadening of the action potentials and prolongation of transmitter release. Due to the strong expression of *KCNA1* in basket cells of the cerebellum, an imbalance between inhibitory and excitatory input could well destabilize motor control under stress or exercise and lead to kinesiogenic ataxia. Independently, myokymia may result from repetitive firing of affected peripheral motoneurons due to potassium current reduction which slows repolarization and hinders hyperpolarization after the action potential.

Adequate treatment, as expected for neuronal hyperexcitability, consists of anticonvulsants such as carbamazepine. Interestingly, kinesigenic attacks also respond to some extent to acetazolamide.

Neuronal calcium channelopathies

A dominantly inherited disease, episodic ataxia-type 2 (EA2), clinically related to EA1, has been described. Patients present with attacks of ataxia triggered by emotional or alimentary stimuli and lasting for hours accompanied, by headaches and cerebellar signs such as vertigo and dysarthria. In the interictal interval spontaneous or gaze nystagmus may be observed. Matching the concomitant symptoms of EA2 patients, a familial form of headache, hemiplegic migraine (FHM) has been shown to be allelic. Individuals affected by this autosomal dominant disorder present with characteristic unilateral migrainous headaches accompanied by nausea, phono- and photophobia. Episodes are typically precipitated by an aura with symptoms of both hyper- and underexcitability such as aphasia, dysarthria, vertigo, homonymous hemianopsia, cheiro-oral paresthesia, and hemiparesis. Some families additionally present with epilepsy, retinal degeneration, hypokusis, persistent cerebellar dysfunction and Purkinje cell atrophy. A progressive form of ataxia not involving the brainstem or retina in the neurodegenerative process, spinocerebellar ataxia (SCA6), is also allelic.

The underlying genetic cause of all three disorders are mutations in *CACNA1A,* encoding the α_1 subunit of the voltage-gated P/Q-type neuronal calcium channel. Remarkably, the three allelic phenotypes are each associated with a different type of mutation: while FHM is caused by missense point mutations suggesting change in function as pathogenetic mechanism, EA2 mutations all lead to

Table 1 Skeletal muscle and neuronal voltage-gated channelopathies (*AR* autosomal recessive, *AD* autosomal dominant)

Disease entity	Locus, chromosome	Gene and gene product	Symptoms
Skeletal muscle voltage-gated channelopathies			
Myotonia congenita of Becker and Thomsen	7q35	*CLCN1* chloride channel	AD (Becker), AD (Thomsen); generalized myotonia, warm-up phenomenon, muscle hypertrophy, transient weakness (Becker)
Paramyotonia congenita	17q23	*SCN4A* sodium channel α subunit	AD; paradoxical myotonia, cold-induced muscle stiffness followed by weakness/paralysis
Potassium-sensitive myotonia	17q23	*SCN4A* sodium channel α subunit	AD; generalized myotonia of variable severity, aggravation by potassium administration, no weakness
Hyperkalemic periodic paralysis	17q23	*SCN4A* sodium channel α subunit	AD; episodic attacks of mainly generalized weakness, hyperkalemia during episode, triggering by rest after body exertion or potassium intake
Hypokalemic periodic paralysis	1 q32	*CACNA1S* dihydropyridine receptor calcium channel α_1 subunit	AD; episodic attacks of mainly generalized weakness, hypokalemia during episode, triggering by carbohydrate rich food or exercise
Malignant hyperthermia	19q12–q13	*RYR1* calcium release channel, ryanodine receptor	AD; triggering by volatile anesthetics or depolarizing muscle relaxants, generalized muscle rigidity, hyperthermia, metabolic acidosis, rhabdomyolysis
	1q32	*CACNA1S* dihydropyridine receptor calcium channel α_1 subunit	
Central core disease	19q12–q13	*RYR1* calcium release channel, ryanodine receptor	AD; congenital myopathy with characteristic histological central cores, muscle hypotonia, proximal weakness, creatine kinase elevation, and susceptibility to malignant hyperthermia
Neuronal voltage-gated channelopathies			
Benign neonatal convulsions	20q13	*KCNQ2* potassium channel α subunit	AD; generalized epileptic seizures, onset in first week of life, remission within the first 6 months of life, normal intellectual development, normal interictal EEG
	8q	*KCNQ3* potassium channel α subunit	
Generalized epilepsy with febrile seizures	19q13.1	*SCNIB* sodium channel β subunit	AD; febrile seizures with onset in first year of life, continuing of febrile and afebrile generalized seizures (tonic-clonic, myoklonic, astatic, absence, atonic) at least until puberty
Episodic ataxia 1	12p13	*KCNA1* potassium channel α subunit	AD; kinesigenic episodes of cerebellar ataxia of minute duration, interictal myokymia
Episodic ataxia 2	19p13	*CACNA1A* P/Q-type calcium channel α_1 subunit	AD; stress-induced episodes of cerebellar ataxia and vertigo of hour duration, interictal nystagmus, cerebellar atrophy
Familial hemiplegic migraine	19p13	*CACNA1A* P/Q-type calcium channel α_1 subunit	AD; migraine with hemiplegic aura, onset in childhood, cerebellar atrophy
Spinocerebellar ataxia type 6	19p13	*CACNA1A* P/Q-type calcium channel α_1 subunit	AD; slowly progressive cerebellar ataxia with nystagmus, vertigo, gait disorder and cerebellar atrophy

changes in posttranscriptional splicing or premature truncation which corresponds to loss of function and haploinsufficiency to be pathogenetically important. In contrast, the progressive disease SCA6 is associated with a trinucleotide expansion in the coding region as shown for several other neurodegenerative disorders.

Altered channel function has been described, a change in single channel properties perhaps being the decisive factor and explaining a depolarizing tendency of the mutant. Until now, even though the functional disturbance of the channel is known, disease pathogenesis has not been deduced because the significance of the channel for the neurons has not been clarified. Of the three disorders, only for FHM and migraine in general has a model for pathogenesis been proposed: spreading depression (a spreading wave of long-lasting depolarization) which could well explain the aura initiating the attacks and be caused by defects of channel function. If, as suggested, *CACNA1A* is more of an aura gene than a true migraine (pain) gene, the headache may only be a secondary (!) effect of the primary defect.

Conclusion

Current research (employing short-cuts derived from experience in the past to accelerate genetic studies by the candidate gene approach) take advantage of the fact that ion channelopathies share many common features such as the attacklike symptoms of hyper- or underexcitability provoked by typical factors, additional progressive components related to cell degeneration, both associated with sustained membrane depolarization (for overview of channelopathies see Table 1). Recurrent patterns of pathogenesis mechanisms associated with the mode of transmission already indicate functional consequences such as recessive mutations leading to loss of function and dominant mutations leading to change in function in the sense of gain of function (dominant *positive* effect) or loss of function (dominant *negative* effect in multimeric proteins or haploinsufficiency). Judging from the numerous ion channel genes cloned to date, multiple forms of disease genetically related to ion channels may be expected in the future which can serve as a model for understanding disease pathogenesis, also of more frequent nonhereditary idiopathic variants.

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