PERGAMON

Neuromuscular Disorders 7 (1997) 127–132

Workshop Report

Paramyotonia, potassium-aggravated myotonias and periodic paralyses. 37th ENMC International Workshop, Naarden, The Netherlands, 8–10 December 1995

1. Introduction

The first ENMC Workshop on myotonias and periodic paralyses was held in October 1992 in Ulm, Germany [19]. Both, Na^+ and Cl^- channel diseases were the subjects. At that time, the existence of a Ca^{2+} channel disease was yet unknown. Since then, the new knowledge to be summarized and the open questions to be discussed had so increased that the organizers of the second Workshop (Reinhardt Rüdel and Frank Lehmann-Horn) decided to concentrate on Na^+ and Ca^{2+} channel diseases, and leave Cl^- channel diseases for another occasion. The meeting was held from the 8 to 10 December 1995 in Naarden, The Netherlands, and was organized in four sessions, the first two of them being devoted to the muscle Na^+ channel and the hereditary diseases associated with it, i.e., paramyotonia congenita (PC), potassium-aggravated myotonia (PAM) and hyperkalemic periodic paralysis (HyperPP). The last two sessions were devoted to the muscular L-type Ca^{2+} channel and the major hereditary disease associated with it, i.e., hypokalemic periodic paralysis (HypoPP). The workshop began with a hearty welcome on behalf of ENMC by Alan E.H. Emery, ENMC's Director of Research.

2. Muscle sodium channel diseases

The 'classical' Na^+ channel diseases are PC and HyperPP. Only when molecular biology was included in the arsenal of methods for research into muscle diseases with disturbed excitability, it turned out that patients who had previously been diagnosed as having 'abnormal forms' of myotonia congenita, a disease now known to be linked to the gene encoding the muscle Cl channel, had in fact a third kind of Na^+ channel disease. Various mutations in *SCN4A*, the gene encoding hSkMl, the α subunit of the adult human skeletal muscle Na^+ channel, may lead to this third kind of Na^+ channelopathy which may even be subdivided according to the severity of the myotonia. It is different from PC by the fact that the symptoms do not show the cold sensitivity typical for PC. It is different from HyperPP by the absence of the symptom of weakness. Its prominent symptom is that the stiffness is much more pronounced after the patients have ingested potassium-rich food. Hence the disease was given the name 'potassium-aggravated myotonia'. The mild form was called myotonia fluctuans [31], the severe form myotonia permanens [21]. Later in the session, Louis Ptáček reported that also in acetazolamide-responsive myotonia [30] the myotonia fluctuates and that the severity of the myotonia is aggravated by potassium. Thus, this disease may be considered as a third form of potassium-aggravated myotonia.

The clinical and molecular biologic description and classification of the Na^+ channel diseases, in particular of PAM, given by Frank Lehmann-Horn, triggered off an extensive and almost emotional discussion on the correct names and classification of the whole group of Na^+ channel diseases. The resulting nomenclature and differential diagnostic procedures are given in the Appendix A to this Report.

Nineteen disease-causing mutations have been identified to date in *SCN4A* (recent review [18]). Eight of them result in PC, 5 in HyperPP and 6 in PAM. Reinhardt Rüdel discussed these mutations with respect to the frequency of the mutated nucleotides. A systematic investigation of spontaneous point mutations causing human genetic disease disclosed that the dinucleotide CpG (p denotes cytosine 5′ to guanine 3′ binding) is a 'hot spot' for mutations [8]. This has been explained to result from the hypermutability of methylated CpG, deamination of 5-methylcytosine (5 mC) to thymidine in this doublet giving rise to $C \rightarrow T$ or $G \rightarrow A$ mutations depending upon in which strand the 5 mC is mutated [9]. Thymidine being a 'normal' nucleoside is

PII S0960-8966(96)00418-X

thought to be less readily detectable and removable by cellular repair mechanisms. Evaluation of 139 point mutations causing human genetic diseases other than Na^+ channelopathies, and consistent with methylation-mediated deamination of 5 mC, yielded 21 CG→TG and 23 CG→CA mutations, i.e., a total of 44 or 31.7% [8]. Of the 19 *SCN4A* mutations, 8 (>40%) contained a mutated base in the CpG dinucleotide. Thus, the frequency of CpG mutations in *SCN4A* corresponds well with that found in general for disease-causing point mutations. With the exception of the 'Ravensberg' families (R1448H, [26]), a founder effect for the mutations could be excluded [34]. Considering the number of independently originating *SCN4A* mutations in 94 non-related families, 60 concerned the CpG dinucleotide. Thus, the percentage of mutations in a CpG nucleotide in *SCN4A* is even higher, i.e. around 64% of the total number. Second in frequency amongst the human disease-causing point mutations [8] were those affecting a GG dinucleotide. Interestingly, mutations of this type are responsible for the three mutations for the amino acid G1306 A/V/E in the supposed inactivation gate [12].

One of the biggest challenges arising for the basic scientist from these natural disease-causing mutations in *SCN4A* is the elucidation of the structure-function relations of the channel protein. Heterologous expression and electrophysiological investigation of various mutant Na^+ channels revealed that in every case the most profound effect was on channel inactivation. Al George Jr. now reported results from recent experiments with the PC-causing L1433R mutation [16]. L1433 is adjacent in the secondary structure to the R1448C/H mutations in IV-S4 which produce their effects largely due to the loss of a positive charge. In contrast, the effects of L1433R are mediated by a change of the hydropathy of the side chain. The two mutations differ in their effects on recovery from inactivation, conditioned inactivation, and steady-state inactivation of the Na^+ channel. Decisive results were obtained with a double mutant containing both L1433R and R1448C. They closely resembled those with R1448C with respect to alterations in the kinetics of inactivation during depolarization and voltage dependence, but they were indistinguishable from L1433R results in the kinetics of recovery from inactivation and steady-state inactivation. No additive effects were seen, suggesting that the two segments S3 and S4 interact during gating. The results suggest that the two segments play distinct roles in different processes of Na^+ channel gating: IV-S4 is critical for the deactivation and inactivation of the open channel while IV-S3 has a dominant role in the recovery of inactivated channels. The two segments interact during the entry to, and exit from, inactivation states.

The following contribution, given by Jens Timmer, led to a more general biophysical question, namely the extraction of information on a channel's structure and function from electrophysiological single-channel data obtained in patch-clamp experiments. Statistical analyses according to Markov models have long been successfully used to estimate rate constants and to test for possible gating schemes [15]. The major drawback of Markov models is that they need an idealized record that can only be obtained by thorough low-pass filtering of the experimental data. By this process, the time resolution is reduced and valuable information may get lost. Hidden Markov models, in contrast, treat noise of ion channel data explicitly and thus allow one to analyze the unfiltered data with improved time resolution [2].

After this excursion into the theoretical fields ploughed by the channel biophysicists, Nenad Mitrovic returned to the Na^+ channel and discussed the functional consequences of four point mutations causing PAM [21,27], and another point mutation causing a severe form of PC [23]. When studied in patch-clamped human embryonic kidney (HEK-293) cells, all PAM-generating mutant channels conducted Na^+ currents that showed abnormal inactivation properties. With regard to controls (i) the decay was slowed, (ii) the non-inactivating component was increased and (iii) the position of the steady-state inactivation (h_∞) curve was slightly shifted towards less negative potentials. All these changes increase excitability and therefore favor myotonia. The PC-causing mutation R1448P was studied in both native human skeletal muscle and heterologously expressed in HEK cells. Again, changes in the inactivation parameters were the most prominent finding, but in contrast to G1306E, the mutation resulting in the most severe form of PAM, the position of the steady-state inactivation curve was slightly shifted towards more negative potentials. In comparison to G1306E, inactivation of the PC-generating mutant R1448P was 2–3 times slower. This may explain why the clinical symptom of paradoxical myotonia (myotonia increasing with continued activity) occurs in PC but not in PAM. The muscle weakness in cold environment in PC (absent in PAM) might be explained by the combination of the left-shift of the h_∞ curve, decreasing the number of available Na^+ channels for an action potential and frequent late re-openings of Na^+ channels, increasing with cooling.

Pronounced potassium sensitivity is the sign of HyperPP and PAM. Mutant channels responsible for either disease never showed potassium sensitivity when expressed in heterologous systems [6]. However, myotubes from patients were claimed to show potassium sensitivity [7]. Steve Cannon now presented results obtained with myotubes from Quarter horses having

equine HyperPP [6]. The ratio of steady-state to peak open probability increased threefold when $[K^+]_e$ was increased from 0 to 10 mM, whereas in normal Na^+ channels this parameter was invariant with $[K^+]_e$. Mutations near the extracellular mouth of the pore can slow the decay of macroscopic Na^+ currents. Thus, changes in $[K^+]_e$ could conceivably alter the gating kinetics of mutant Na^+ channels [5]. Most probably, however, the potassium sensitivity in patients is mainly caused by the potassium-induced depolarization causing increased late openings of the Na^+ channels [21].

To conclude the second Na^+ channel session, Bertrand Fontaine was asked to report his recent linkage studies of Schwartz-Jampel syndrome (SJS), as the symptoms of this disorder have some similarities with those of the Na^+ channelopathies. Using homozygosity mapping, a large group of mainly Tunisian and French researchers have localized the SJS locus to chromosome 1p34–p36.1 in an 8 cM interval flanked by markers D1S199 and Dl 5234. Families of different ethnic background showed genetic linkage to the same locus. Genetic homogeneity is suggested [28].

3. L-type calcium channel diseases

Perhaps the most important progress in the research of pathogenesis of myotonias and periodic paralyses since the Ulm Workshop in 1992 [19] was the linkage of hypokalemic periodic paralysis (HypoPP) to *CACLN1A3*, the gene encoding the voltage-gated L-type Ca^{2+} channel (DHP-receptor), and the detection of three disease-causing mutations in this gene. The disease is the most common form of hereditary periodic paralysis with a frequency of about 1:100 000.

The session began with the clinical and neurophysiological description of the very family in which Biemond and Polak Daniels had 1934 detected the hypokalemia during the attacks of paralysis [3]. Thera Links and JH van der Hoeven had followed 280 family members over 5 generations [24]. They reported that penetrance was 80% in women. Two of the patients had died during attacks. An interesting observation was that many of the patients had fluctuating strength even in the attack-free interval. All of them presented permanent weakness when they became old.

Several animal models of HypoPP have been detected, the most thoroughly studied being the Burmese cat. Timm Gruffydd-Jones at the Bristol School of Veterinary Science has seen several of these cats over the past 10 years. He reported that they present with signs of intermittent muscle weakness, dramatic ventral neck flexion, fore- and hindlimb lameness and a hunched sitting posture. Attacks may be precipitated by exercise and can persist for up to 3 weeks. Some kittens had died while showing acute clinical signs, whereas others had resolved without treatment. An intermittent hypokalemia mirrored the episodic nature of the clinical signs [4]. The defect is not yet known on the molecular level.

Bertrand Fontaine, one of the key persons in the team finding the genomic linkage of HypoPP, then gave an account of these results [11]. A systematic genome-wide search in members of three families had demonstrated that the disease is linked to chromosome 1q31–32 and cosegregates with the gene encoding the L-type Ca^{2+} channel (DHP-receptor) $\alpha 1$ subunit. No founder effect was noted. Sequencing of cDNA derived from muscle biopsies of patients revealed so far three mutations. Two of these mutations are analogous predicting arginine to histidine mutations within the highly conserved S4 regions of repeats II and IV (R528H and R1239H, respectively), the third predicts an arginine to glycine mutation in IV-S4 (R1239G) [17,29]. The mutations have corresponding counterparts in the α subunit of the Na^+ channel and those cause paramyotonia congenita by uncoupling activation from inactivation. The majority of families carry either the R528H or the R1239H mutation. Interesting discrepancies were found with respect to gene penetrance. In one of the families having the R528H mutation, penetrance was 100% in men and 80% in women, whereas in no family with the R1239H mutation reduced penetrance in females was noted. In the large family reported by Thera Links incomplete penetrance was noted for both men and women.

Following the clinical and genetic presentations, the cellular physiology of the voltage-gated L-type Ca^{2+} channel was introduced by Franz Hofmann who focussed on the sites of drug interaction with the channel molecule (see also his review [13]), and by Werner Melzer who described the unique dual role of the skeletal muscle DHP receptor as a voltage-dependent ion channel and as a voltage sensor for the activation of internal Ca^{2+} release via the ryanodine receptor (review [25]). He also pointed out that the proposed tetradic arrangement of DHP receptors in the SR-T-tubular junction might form the basis of the dominant inheritance of HypoPP.

The session was completed by Klaus Schleifer who presented his structural calculations of the L-type Ca^{2+} channel. Physiological investigations (reported in the final session, see below) suggest some critical differences in the inactivation parameters between the wild-type and the channel having the R528H mutation in segment S4 of the $\alpha 1$ subunit. This amphipathic membrane-spanning part is probably located in the center of the hydrophobic segments S1–S6 sur-

rounding the pore region. Simulations of the molecular dynamics of the lowest energy conformations and evaluation of the molecular electrostatic potentials reveal a break of the spiral-like, positively charged potential around the helix near the extracellular face at the mutation R528H. This change inside a region considered to be the voltage sensor of the channel could explain the abnormal inactivation behavior.

The final session on the L-type Ca^{2+} channel and HypoPP, was opened by Kirk Hogan who discussed the genomic structure of *CACNL1A3*. The gene contains 44 exons, the cDNA sequence consists of 6167 bp. The transcript consists of 1873 amino acids with a calculated molecular mass of 212.3 kDa. The protein exhibits 92% identity to the rabbit skeletal muscle, and 65% identity to the human cardiac and smooth muscle. The β subunit has been shown to bind to a conserved motif in the cytoplasmic linker of the rat $\alpha 1$ subunit. A similar motif is present in the human *CACNL1A3* polypeptide at position 357–374. There are four potential cAMP-dependent protein kinase (PKA) phosphorylation sites. However, only three are predicted to be in the cytoplasm [14].

Bernhard Flucher reported his structural and functional studies on the development of the junction between transverse tubular system and sarcoplasmic reticulum and of the DHP receptor/ryanodine receptor (RyR) interaction. He showed that DHP receptor $\alpha 1$ subunits and ryanodine receptors are colocalized very early during the development of the junction.

However, junction formation does not necessarily require the presence of these proteins as could be shown in dysgenic (no $\alpha 1$ subunit) and dyspedic (no RyR) myotubes. Ca transients recorded during development undergo characteristic changes; they get larger and faster corresponding to the maturing of the EC coupling process, and two independent components corresponding to voltage and Ca-controlled Ca release could be identified [10].

As regards the pathophysiology of HypoPP, the most interesting open question is: How can a mutation in the Ca^{2+} channel give rise to hypokalemia and paralysis? Istvan Sipos addressed this question reporting his electrophysiological investigations on myotubes derived from HypoPP patients carrying the R528H or the R1239H mutation [20,33]. The steady-state inactivation curve seemed shifted towards more negative potentials in myotubes with the R528H mutation, and the Ca^{2+} current density was reduced in R1239H. In addition, an enhanced Ca^{2+} inward current of rapid kinetics (third-type, see [32]) was detected for both mutations. The pathophysiological mechanisms of hypokalemia and paralysis cannot easily be explained by these first results.

Since for the rabbit cardiac Ca^{2+} channel $\alpha 1$ subunit heterologous expression in HEK cells is well established, Holger Lerche and colleagues [22] had looked for the consequences of the mutation R650H which is in analogous position to the R528H mutation in skeletal muscle. In contrast to results with myotubes from HypoPP patients, there was no shift in steady-state inactivation detectable under various conditions (co-expression of different subunits, pH change, etc.). Co-expression of the skeletal muscle specific γ subunit did produce a negative shift in inactivation, but to the same degree in WT and R650H. Likewise, negative results with the known HypoPP mutations were reported by Kurt Beam, whose group used primary-cultured myotubes from mice with the muscular dysgenesis (mdg) mutation and functionally expressed normal and mutant rabbit skeletal muscle $\alpha 1$ subunits [1].

However, an R1239E mutation was found to abolish Ca^{2+} current by shifting the Ca^{2+} release/voltage dependence by about +15 mV. Other point mutations in the close vicinity showed pronounced effects on inactivation kinetics. At the present stage, the link between the mutations in the DHP receptor and the pathophysiology remains unclear.

Following an extensive general discussion and a sincere thanks by the organizers on behalf of all the participants, the Workshop was closed by Alan Emery.

This Workshop was made possible thanks to the financial support of the European Neuromuscular Center (ENMC) and its main sponsors: Association Française contre les Myopathies, Italian Telethon Committee, Muscular Dystrophy Group of Great Britain and Northern Ireland, Unione Italiana Lotta alla Distrofia Muscolare, Vereniging Spierziekten Nederland as well as its associate members: Schweizer Stiftung für die Erforschung der Muskelkrankheiten, Deutsche Gesellschaft für Muskelkranke and Muskelsvindfonden.

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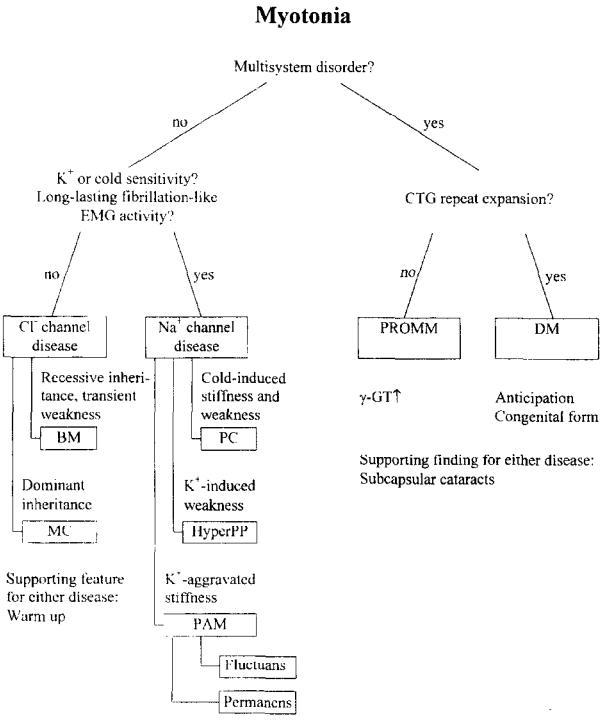
Appendix A. Differential diagnostic scheme

The following flow diagram for the differential diagnosis of a myotonic disease was developed during the first session of the Workshop. Muscle stiffness (myotonia), the first cardinal symptom of myotonic diseases, may be the only or the major symptom (as in Thomsen's myotonia congenita, MC, or in potassium-aggravated myotonia, PAM). It may also be a minor symptom (as in hyperkalemic periodic paralysis, HyperPP, proximal myotonic myopathy, PROMM, and in many cases of myotonic dystrophy, DM.



The second cardinal symptom of myotonic diseases is muscle weakness. Long-lasting weakness (lasting for hours) is known in HyperPP and, after work in the cold, in paramyotonia congenita, PC (patients may also present a combination of the two diseases). Transient weakness lasting only a few seconds is known in Becker myotonia, BM.

Permanent weakness is only known in DM and PROMM. PROMM patients also sometimes report slow fluctuations (periodicity of months) of their muscle strength.

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