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Channelopathies: Summary of the hot topic keynotes session

Jason P. Magby [a,*], April P. Neal [b], William D. Atchison [b], Isaac P. Pessah [c], Timothy J. Shafer [d]

[a] Joint Graduate Program in Toxicology, Rutgers University/University of Medicine and Dentistry New Jersey, 170 Frelinghuysen Rd., Piscataway, NJ, United States
[b] Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI, United States
[c] Department of Molecular Biosciences, School of Veterinary Medicine, University of California, Davis, CA, United States
[d] Integrated Systems Toxicology Division, National Health and Environmental Effects Research Laboratory, Office of Research and Development, US Environmental Protection Agency, Research Triangle Park, NC, USA

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ABSTRACT

The "Hot Topic Keynotes: Channelopathies" session of the 26th International Neurotoxicology Conference brought together toxicologists studying interactions of environmental toxicants with ion channels, to review the state of the science of channelopathies and to discuss the potential for interactions between environmental exposures and channelopathies. This session presented an overview of chemicals altering ion channel function and background about different channelopathy models. It then explored the available evidence that individuals with channelopathies may or may not be more sensitive to effects of chemicals.

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Dr. Tim Shafer began his presentation by defining what channelopathies are and presenting several examples of channelopathies. Channelopathies are mutations that alter the function of ion channels such that they result in clinically definable syndromes including forms of epilepsy, migraine headache, ataxia and other neurological and cardiac syndromes (Kullmann, 2010). Because of the ubiquitous but heterogeneous nature of ion channels, channelopathy syndromes are highly variable, and depend not only on the type of channel mutated but also on how the mutation alters the function of the channel (Waxman, 2007). While there are a number of possible phenotypes resulting from channel mutations, one feature shared by a number of channelopathies is that they cause periodic and discrete attacks, allowing the carrier of the mutation to function normally between attacks (Kullmann, 2010). Like many genetic diseases, channelopathies tend to present early in life; some only cause dysfunction during development, others may continue to cause problems throughout life while others do not present overt (or at least recognized) clinical signs without environmental triggers (Pessah et al., 2010; Striessnig et al., 2010). In order to understand the full implications of these mutations, and their highly variable manifestations, it is essential to understand ion channel physiology and function.

Ion channels are found in all cell types throughout the body, and have a wide variety of structures and functions. Ion channels serve as transmembrane pores that, when open, allow ions to pass across a membrane. Because movement of ions across a membrane results in electrical currents, ion channels serve essential functions in electrically excitable tissues, such as neural cells and cardiac, skeletal and smooth muscle. The opening and closing (gating) of ion channels is controlled either by changes in membrane potential (voltage; Vacher et al., 2008), or by the binding of ligands such as neurotransmitters. Thus, ion channels typically are classified into one of two large groups based on the stimuli that activate them: voltage-gated or ligand gated.

* Corresponding author at: EOHSI 170 Frelinghuysen rd Piscataway NJ 08854, United States. Tel.: +1 7324453754.
E-mail address: magby@eohsi.rutgers.edu (J.P. Magby).

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The voltage-gated ion channel family includes voltage-gated sodium channels, voltage-gated calcium channels, and voltage-gated potassium channels. All of these channels consist of a pore-forming α subunit and associated auxiliary subunits that modify the function and/or expression of the α subunit. Mutations in either the pore forming α subunit or the auxiliary subunits can manifest as clinical syndromes. Voltage-gated sodium channels (VGSC) are responsible for neuronal depolarization as well as initiation and propagation of action potentials in the nervous system. Sodium channel mutations in humans and animals result in seizures, rare forms of familial migraine headache, movement and pain disorders (Catterall, 2000). The voltage-gated calcium channels (VGCC) are essential to cell signaling, neurotransmitter release and neuronal plasticity. Mutations in VGCC channels result in seizures, migraine, neurodegenerative disorders and myasthenic syndromes (Striessnig et al., 2010). The voltage-gated potassium channels are required for neuronal repolarization following the rising phase of the action potential. Potassium channelopathies are also associated with seizures as well as paralysis, depending on the nature of the mutation. In the heart, mutations have been described in the hERG potassium channel ($K_v1.1$) that disrupt its function, leading to a potentially fatal arrhythmia (*torsades de pointes*). The hERG channel has been identified as an unintended target for a number of pharmaceutical agents. In some cases block of this channel can give rise death by cardiac arrhythmia. This has made this channel particularly important in pharmaceutical safety testing (Table 1).

The ligand-gated ion channel family includes nicotinic acetylcholine receptor (nAChR), γ-aminobutyric acid receptor (GABA), glycine, and seratonin receptor ($5\text{-}HT_3$) channels. These channels, as their name implies, open in response to ligand binding, permitting ion flux. Each of these receptors is comprised a homo- or heteromer of 5 receptor subunits, and each subunit has multiple isoforms. The wide variety of subunits that comprise these channels produces a wide variety of functional diversity. The most common manifestation of mutations in these ion channels is epilepsy (Kullmann, 2010). However, the specific type of epilepsy varies depending on the channel and the mutation. These range from childhood absence epilepsy, produced by a dominantly inherited mutation of the beta 3 subunit of the $GABA_A$ receptor which reduces cell-surface

Table 1
Ion channels and selected agents that act on them.

Channel	Gene	Isoform	Diseases[a]	Environmental/pharmacological agents[b]
Sodium channels	SCN1A	$Na_v1.1$ (α subunit)	Epilepsy, migraine	Pyrethroid pesticides, brevetoxins, organochlorine pesticides, volatile organic compounds (e.g. toluene) local anesthetics (e.g. procaine, bupivacaine), anti-convulsants (e.g. phenytoin), antiarrhythmic agents (e.g. procainamide)
	SCN1B	β1	Epilepsy	
	SCN2A	$Na_v1.2$ (α subunit)	Epilepsy	
Potassium channels	KCNQ2	$K_v7.2$	Epilepsy	Apitoxin, antiarrhythmic agents (e.g. amiodarone)
	KCNQ3	$K_v7.3$	Epilepsy	
	KCNMA1	BK	Epilepsy with dyskinesia	
	KCNA1	$K_v1.1$	Episodic ataxia	
	KCNC3	$K_v3.3$	Ataxia	
Calcium channels	CACNA1H	α1H subunit of $Ca_v3.2$	Epilepsy	Mercury (including methylmercury), lead, cadmium, nickel cobalt, pyrethroids antihypertensives (e.g. dihydropyridines), antiarrhythmic agents (e.g. verapimil)
	CACNA1A	α1A subunit of $Ca_v2.1$	Episodic or progressive ataxia, migraine, epilepsy	
$GABA_A$ receptors	GABRA1	α1	Epilepsy	Phenylpyrazoles, proconvulsant drugs. Sedatives (benzodiazepines, ethanol), cyclodiene insecticides (e.g. lindane), RDX, volatile organic compounds (e.g. toluene), metals including mercury, antianxiolytics, muscle relaxants and volatile anesthetics
	GABRB3	β3	Epilepsy	
	GABRG2	γ2	Epilepsy	
Nicotinic ACh receptors	CHRNA2	α2	Epilepsy	Nicotine, neonicotinoid pesticides, volatile organic compounds (e.g. toluene) paralytic drugs, antidepressant, antismoking drugs
	CHNRA4	α4	Epilepsy	
	CHRNB2	β2	Epilepsy	
Glycine receptors	GLRA1	α1	Hyperekplexia	Phencyclidine, volatile organic compounds (e.g. toluene) and ketamine
RYR receptor	RYR1		Malignant hyperthermia, congenital myopathy	PCBs, caffeine, volatile anesthetics
	RYR2		Arrhythmogenic disorders	

[a] This column lists examples of diseases or clinical syndromes that have been linked to mutations in this ion channel subunit.
[b] This column lists examples of environmental and/or pharmacological agents that are known to interact with these channels. These lists of examples may not include all compounds known to act at a given channel type.