Queer Currents, Steady Rhythms, and Drunken DA Neurons. Focus on “Hyperpolarization-Activated Cation Current (I_h) Is an Ethanol Target in Midbrain Dopamine Neurons of Mice”

Carl R. Lupica1 and Mark S. Brodie2

1Electrophysiology Section, Cellular Neurobiology Branch, National Institute on Drug Abuse Intramural Research Program, National Institutes of Health, Department of Health and Human Services, Baltimore, Maryland; and 2Department of Physiology and Biophysics, University of Illinois at Chicago, College of Medicine, Chicago, Illinois

Currents derived from hyperpolarization-activated cation channels (I_h channels) were once referred to as “queer currents (I_q)” because they were unusual in their large amplitudes, their activation by hyperpolarization, and their lack of inactivation during sustained hyperpolarization of the cellular membrane (Halliwell and Adams 1982). Today, we know that I_h channels are voltage-dependent ion channels that gate K^+ and Na^+ and are derived from at least four genes (hyperpolarization-activated cyclic nucleotide-sensitive cation nonselective, HCN 1–4) found throughout the brain (Biell et al. 1999; Ludwig et al. 1998; Santoro et al. 1998). The expression of homomeric ion channels from these genes revealed distinct biophysical properties, and different sensitivities to cyclic AMP (cAMP) (Ludwig et al. 1998, 1999; Santoro et al. 1998, 2000). One of the earliest suggested roles for I_h channels followed from their discovery in intrinsically rhythmic sinoatrial and Purkinje cells of the heart, implying a contribution to oscillatory pacemaker activity (Brown and DiFrancesco 1980; DiFrancesco 1981; Yanagihara and Irisawa 1980). This role was also confirmed in neurons after it was discovered that these ion channels were expressed throughout the CNS (see Pape 1996 for review). One of the more thoroughly studied pacemaker roles for I_h is found in thalamic relay neurons where it acts in concert with low-threshold Ca^{2+} channels to generate rhythmic activity (McCormick and Pape 1990b) that is modulated by G-protein-coupled receptors regulating intracellular concentrations of cAMP (McCormick and Pape 1990a). In this issue of Journal of Neurophysiology (p. 619–626), a study by Okamoto et al. (2006) illustrates another role for I_h as a target for ethanol in rhythmically firing dopamine (DA) neurons in the ventral tegmental area (VTA) and also hints at the potential importance of I_h in regulating the rewarding properties of other abused drugs as well as natural environmental stimuli.

The DA neurons found in the VTA and the substantia nigra pars compacta (SNc) of the ventral mesencephalon are known to fire in a pacemaker-like fashion and in more complex burst firing modes (Overton and Clark 1997). These neurons have received a great deal of attention because of the obligatory role they play in signaling the strength and timing of environmental rewards and in mediating the actions of abused drugs. Because I_h channels, derived primarily from HCN-2 gene expression (Notomi and Shigemoto 2004; Santoro et al. 2000), mediate large currents in these neurons, their contribution to the firing patterns of these cells and in mediating the rewarding properties of abused drugs have been a source of interest. In further support of this idea, recent work has demonstrated that blockade of this current in VTA DA neurons alters their pacemaker discharge rates in vitro (Seutin et al. 2001).

Ethanol is an abused drug that appears to signal at least part of its rewarding effects in animals and humans through the elevation of extracellular DA in the terminal fields of the VTA DA neurons in the NAc (Di Chiara and Imperato 1988). Furthermore, electrophysiological studies in intact animals and in VTA brain slices suggest that this occurs through the augmentation of action potential discharge rates of VTA DA neurons rather than via actions at DA axon terminals (Brodie and Appel 1998; Brodie et al. 1990; Budygin et al. 2001; Mereu et al. 1984). The importance of the VTA in mediating rewarding effects of ethanol is further suggested by the observation that rats will self-administer ethanol directly into the VTA under operant schedules of reinforcement (Rodd et al. 2004). Several indirect mechanisms have been proposed to account for the ability of ethanol to increase DA firing rates, including their disinhibition via a reduction in GABAergic function (Grobin et al. 1998). However, more recent in vitro studies suggest that the ethanol effect occurs via direct actions on DA neurons because the excitation was observed in acutely isolated DA neurons in which the synaptic contacts were eliminated by the dissociation process (Brodie et al. 1999).

An early indication that the mechanism of the ethanol-induced increase in VTA DA neuron firing might be through the enhancement of I_h came from an in vitro current-clamp study by Brodie and Appel (1998) that showed that this occurred at intoxicating levels of ethanol. However, this group also reported that the blockade of I_h had no effect on the ability of ethanol to increase VTA DA neuron excitability in vitro (Appel et al. 2003). The study by Okamoto et al. (2006) confirms the depolarizing shift in the voltage dependency of I_h by ethanol in VTA DA neurons and suggests that it may represent an important cellular mechanism in mediating the rewarding effects of this ubiquitously consumed drug. In this study, Okamoto et al. (2006) report that the augmentation of I_h by ethanol was accompanied by an increase in DA neuron firing rates and that both effects could be eliminated by the I_h blockers, ZD 7288, or cesium. Also, the change in I_h caused by ethanol was mediated by increased cAMP, whereas an apparent increase in the maximal I_h current by ethanol occurred independently of changes in cAMP. Another important finding of the study by Okamoto et al. (2006) was that repeated exposure to intoxicating levels of ethanol reduced the baseline...
density of $I_h$ and the ability of acute ethanol to increase VTA DA neuron firing rates, suggesting that changes in $I_h$ may underlie tolerance to this drug, and that this may be related to the neurobiological adaptations associated with alcoholism.

Although the observation that $I_h$ blockade by ZD7288 reduced the ethanol-induced excitation is contrary to the findings of Appel et al. (2003), the disparate results may be explained by the species of rodent used in these in vitro studies (Fisher 344 rats vs. C57BL/6 mice) or the use of coronal versus horizontal VTA brain slices. However, despite this inconsistency, both groups agree that ethanol shifts the voltage dependency of $I_h$ so that it is more active near the resting membrane potential of the DA neuron. From this, it seems plausible that part of the rewarding effects of ethanol could be mediated through its actions on $I_h$ in these neurons, particularly in vivo, where the synaptic inputs to these cells are intact and strong synaptic inhibition can be encountered.

Finally, one of the more intriguing findings in the study by Okamoto et al. (2006) was that repeated exposure to ethanol resulted in tolerance to its ability to increase VTA DA neuron firing rates and to cause a large reduction in $I_h$ density in these cells. Although there have been a number of roles ascribed to $I_h$ in central neurons, one that may be particularly relevant to chronic ethanol’s reduction in $I_h$ density may be found in the ability of $I_h$ to modify the strength of synaptic inputs by altering dendritic membrane resistance (Magee 1998). The significance of this role of $I_h$ can be seen in the increased inhibition of VTA DA neurons by DA-D2 receptors when $I_h$ channels are blocked by ZD7288 (Liu et al. 2003). By analogy, a reduction in $I_h$ strength by long-term ethanol exposure may alter the strength and integration of excitatory and inhibitory synaptic inputs to the DA neurons, thereby “re-setting” the baseline responsiveness of these cells to these inputs. In turn, this re-setting of DA neuron sensitivity to synaptic input will likely alter firing rates and may result in an altered allostatic state, leading to an increased vulnerability to ethanol abuse (Koob 2003). As a result, by producing a lasting reduction in $I_h$ density in these critical VTA DA neurons, repeated ethanol exposure may increase liability for the development of alcoholism and may also increase vulnerability to addiction to other abused drugs. Thus the findings reported by Okamoto et al. (2006) may help us understand the effects of ethanol on brain reward circuits and may extend well beyond to provide insight into a critical mechanism for the alteration of the reward system by other abused substances.

**References**


