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Ethanol and acetaldehyde action on central dopamine systems: Mechanisms, modulation and relationship to stress

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Abstract

There has been a great deal of activity in recent years in the study of the direct effects of ethanol on the dopamine reward system originating in the ventral tegmental area (VTA). In addition, recent evidence suggests that acetaldehyde formed from ethanol in the brain or periphery may be a crucial factor in the central effects of ethanol. This critical review examines the actions of ethanol and acetaldehyde on neurons of the VTA and the possible interactions with stress, with a focus on electrophysiological studies *in vivo* and *in vitro*. Ethanol has specific effects on dopamine neurons and there is recent evidence that some of the *in vivo* and *in vitro* effects of ethanol are mediated by acetaldehyde. Stress has some analogous actions on neuronal activity in the VTA, and interactions between the effects of stress and alcohol on VTA neurons may be a factor in ethanol-seeking behavior. Taken together, the evidence suggests that stress may contribute to the activating effects of ethanol on dopamine VTA neurons, that at least some actions of ethanol on dopamine VTA neurons are mediated by acetaldehyde, and that interaction between stress and alcohol could play a role in susceptibility to alcoholism. The link between acetaldehyde and ethanol actions on brain reward pathways may provide a new avenue for development of agents to reduce alcohol craving.

Keywords

alcohol; dopamine; VTA; electrophysiology; catalase

Introduction

While ethanol is a substance widely abused throughout the world, the mechanisms of action of this drug on brain neurons are only beginning to be elucidated, and it is clear that those

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effects are numerous and varied. Ethanol has been shown to act on a number of neurotransmitter receptors, including GABA and glutamate receptors, to act directly on a number of ion channels, including calcium channels (Wang et al., 1992), h-current (I_h) (Brodie and Appel, 1998), and several potassium channels including BK (Chu et al., 1998), GIRK (Lewohl et al., 1999) and Mchannels (Koyama et al., 2007; Moore et al., 1990). It also acts on second messenger systems, with actions, for example, on some isoforms of adenylate cyclase (Saito et al., 1985; Yoshimura and Tabakoff, 1999) and protein kinase C (Messing et al., 1990; Messing et al., 1991; Solem et al., 1997). As the field progresses, few of the possible candidates are winnowed out, and new possibilities in different brain areas are discovered. The challenge of the next century will be to identify those factors which are important in specific aspects of alcoholism (e.g., stress-induced reinstatement of alcohol self-administration), and how modulation of those ethanol-sensitive factors (increasing or decreasing) can prevent or reduce the disease state.

One brain system that is important for rewarding or reinforcing effects of numerous drugs of abuse is the dopamine reward system (Ikemoto and Wise, 2004; Koob, 2003). Dopamine has been linked to self-administration of most drugs of abuse, and drugs abused by humans increase dopamine output in target regions of the brain (Di Chiara and Imperato, 1988; Volkow et al., 2007). Importantly, the dopamine system seems to be tonically reduced after chronic treatment and withdrawal from many abused chemicals including alcohol (Melis et al., 2005). As dopamine has also been linked to stress (for review see Marinelli, 2007), and there is evidence for interaction between stress and drug self-administration (Kreek and Koob, 1998; Shaham et al., 2000; Sinha, 2001; Wise, 2008) , it is important to consider the effects of ethanol directly on the dopamine systems of the brain, specifically the mesolimbic and mesocortical systems originating in the VTA and terminating in the nucleus accumbens (NAc) and prefrontal cortex, respectively. Finally, it should be considered that there are individual differences in dopamine cell response (Brodie and Appel, 2000; Wanat et al., 2008b) that could alter the response to stress and to ethanol.

Acute ethanol effects on dopaminergic neurons of the VTA

Dopamine neurons of the VTA appear to play a critical role in processes involved in addiction. Whether it is assessment of salience of reinforcing environmental cues (Mirenowicz and Schultz, 1996) or facilitation of plasticity in target regions (Durstewitz et al., 2000; Gonzalez-Burgos et al., 2002; Lapish et al., 2006), it is clear that dopaminergic neurotransmission is important in processes leading to addiction. The dopamine neurons of the VTA are thought to be the source of dopamine for the NAc and prefrontal cortex (Oades and Halliday, 1987).

Ethanol was shown to cause excitation of dopamine VTA neurons *in vivo* by Gessa and associates (Gessa et al., 1985b; Mereu et al., 1984). Ethanol caused a dose-dependent increase in the spontaneous firing rate of dopamine VTA neurons of rats. Interestingly, the dose-response curve for alcohol-induced activation of dopamine VTA neurons was to the left of the dose-response curve for alcohol-induced activation of dopamine neurons of the substantia nigra (Gessa et al., 1985b). These results suggested a preferential stimulation of dopamine VTA neurons, and helped support the role of these neurons in drug-induced reinforcement. Likewise, it was shown that systemic administration of many abused substances, including ethanol, caused an increase of dopamine levels in the NAc, another factor in linking the mesolimbic dopamine system to reward (Di Chiara and Imperato, 1988; Imperato and Di Chiara, 1986). Early behavior experiments demonstrated that dopaminergic drugs could alter ethanol-related behaviors related to reward and reinforcement, again supporting the link between dopaminergic neurotransmission and alcohol (Pfeffer and Samson, 1985; Pfeffer and Samson, 1986; Pfeffer and Samson, 1988). More recent experiments have shown that rats will self-administer ethanol directly into the VTA (Rodd et al., 2004a).

Ethanol caused concentration-dependent increases in spontaneous action potential firing of dopamine VTA neurons, and the excitation persisted in medium that blocked synaptic transmission, indicating that ethanol was acting on the dopamine neurons themselves (Brodie et al., 1988). A later study used acutely dissociated dopamine VTA neurons that were enzymatically treated to strip them of synaptic endings and found ethanol-induced excitation of these acutely dissociated neurons, again indicating a direct effect of ethanol on these dopamine neurons (Brodie et al., 1999). These studies certainly do not rule out actions of ethanol in the intact animal that may contribute to the excitation (such as has been suggested by others (Gessa et al., 1985a; Stobbs et al., 2004)), but they demonstrate that such interactions are not necessary, and in addition, they demonstrate that reduced systems can be used to study the excitatory action of ethanol on these neurons.

Long-chain alcohols, as well as trichloroethanol (the active metabolite of the general anesthetic chloral hydrate), also increase the spontaneous activity of dopamine VTA neurons (Appel et al., 2006). Interestingly, repeated chronic ethanol treatment results in an increase in the excitatory effect of ethanol on mouse dopamine VTA neurons (Brodie, 2002), and an increased bursting response to NMDA associated with a reduction in SK currents and h-currents in DA VTA neurons, as well as increased bursting in response to NMDA (Hopf et al., 2007).

As the ethanol-induced excitation can be seen in acutely dissociated neurons, it suggests a site of action either on the cell surface or mediated by intracellular constituents, such as second messengers. Studies of the effects of ethanol on ion channels have demonstrated that ethanol can have direct actions on ion channels such as BK (Chu et al., 1998). Investigations of ion channel blockers on the effects of alcohol in the VTA revealed that ethanol-induced excitation could be blocked with quinidine, at concentrations which block primarily potassium channels (Appel et al., 2003). There are a large variety of potassium currents blocked by quinidine, one of which is M-current. In a study done primarily in acutely dissociated neurons, it was shown that ethanol reduced M-current, and that blockade of M-current with a selective M-channel antagonist (XE991) produced excitation (Koyama et al., 2007). By comparing the ratio of M-current blockade to excitation produced by ethanol and XE991, the conclusion drawn was that ethanol indeed blocks M-current, but additional currents are likely also involved in the excitatory effects of ethanol (Koyama et al., 2007). One study in mouse dopamine VTA neurons suggested that ethanol excitation was mediated by I_h, a current that is blocked by ZD7288 (Okamoto et al., 2006), which would be consistent with the reported acute (Brodie and Appel, 1998) and chronic (Hopf et al., 2007; Okamoto et al., 2006) effects of ethanol on I_h. A more recent study indicated that in the presence of ZD7288, ethanol can increase an inhibitory, barium-sensitive, inwardly rectifying potassium current which opposes ethanol excitation (McDaid et al., 2008).

Acetaldehyde in the brain

Alcohol is converted by the liver to acetaldehyde and the resulting acetaldehyde is converted to acetate by aldehyde dehydrogenase acetate, which then enters the metabolic tricarboxylic acid (TCA) cycle. Following oral administration, ethanol is metabolized into acetaldehyde in the gastric system mainly by alcohol dehydrogenase with a small contribution from other enzymes, such as cytochrome P-450 (CYP2E1) (Edenberg, 2007; Ramchandani et al., 2001).

The acetaldehyde formed in the liver would be expected to have little effect in the brain, as it is prevented from entering the brain by the blood-brain barrier (BBB), but in the central nervous system, ethanol is locally metabolized into acetaldehyde by catalase (Arizzi-LaFrance et al., 2006; Hansson et al., 1999; Jamal et al., 2007). While alcohol metabolism in the brain is dominated by catalase, the microsomal enzyme cytochrome P450 also can convert ethanol to acetaldehyde (Zakhari, 2006). Low doses of alcohol can reduce brain glucose metabolism,

suggesting that the acetate formed by the metabolism of alcohol in the brain and the liver can be used as a source of energy by the brain (Volkow et al., 2006). The acetaldehyde formed from alcohol may also have an effect on monoaminergic neuronal systems, either directly, as proposed below, or indirectly through the formation of condensation products like tetrahydroisoquinolines (THIQs) or beta-carbolines. It is possible that these latter agents can have effects on sensitive brain areas like the VTA, which is involved in the rewarding/ reinforcing effects of alcohol.

Acetaldehyde in the VTA *in vivo*

Recent results from rodent studies largely support the idea that acetaldehyde participates in ethanol's psychoactive effects through its own rewarding properties. Indeed, acetaldehyde induces conditioned stimulus preference (Quertemont and De Witte, 2001) and place preference (Peana et al., 2008). Consistent with these findings is the observation that acetaldehyde is self-administered by rats directly into the posterior VTA (Rodd-Henricks et al., 2002), and directly enhances the activity of putative dopamine neurons in the rat VTA *in vivo* (Foddai et al., 2004). Furthermore, reduction of acetaldehyde (by administration of the acetaldehyde-sequestering agent penicillin-derived sulfhydryl amino acid D-penicillamine (Dp)) strongly sustain the hypothesis that some of the behavioral (Font et al., 2006b) and rewarding (Font et al., 2006a) effects of ethanol are mediated by acetaldehyde. Consistent with this finding, we reported an increase in dopamine outflow following intragastric administration of both acetaldehyde and ethanol which was prevented by peripheral blockade of alcohol dehydrogenase with 4- methyl pyrazole (4-MP) (Melis et al., 2007). In contrast to our findings, it should be noted that a previous microdialysis study (Ward et al., 1997) did not report an increase in microdialysate dopamine after acetaldehyde challenge.

To further characterize the contribution of acetaldehyde on the overall ethanol-induced increase of dopamine in the NAc, we studied the effects of ethanol and acetaldehyde administration in animals pretreated with Dp using both microdialysis and single cell extracellular recordings in antidromically-identified mesoaccumbens dopamine neurons (Enrico et al., 2009). Notably, Dp is able to selectively sequester acetaldehyde, reducing blood acetaldehyde levels without interfering with alcohol metabolism (Enrico et al., 2009; Serrano et al., 2007).We observed that acute administration of both ethanol and acetaldehyde increased dopamine release in the shell of NAc of freely moving rats, as well as neuronal activity in mesoaccumbens dopamine cells in anesthetized animals (Enrico et al., 2009). The stimulating effect of acetaldehyde on dopamine release in the NAc was clear for both intragastric administration and local administration in the VTA, thereby suggesting an intra-VTA action (see also (Melis et al., 2007) for further discussion on this point). The increased release of dopamine by ethanol and acetaldehyde was blocked by the Dp pretreatment (Enrico et al., 2009).

Since the stimulating effect of ethanol on the mesolimbic dopamine system, in both rodents and humans, is a well described phenomenon commonly ascribed to specific properties of ethanol itself, it is particularly interesting that rats pretreated with 4MP (45 mg/kg i.p. 24 hours before ethanol challenge) showed no increase of extracellular dopamine levels in the NAc following ethanol (1 g/kg, i.g.) administration (Diana et al., 2008; Foddai et al., 2004).

As a result of these findings, additional studies were performed to assess the effects of acetaldehyde, administered either by gavage or intravenously (Enrico et al., 2009), on the mesolimbic dopamine system. Acetaldehyde presence in the brain has been a controversial issue. However, several studies demonstrated that systemic administration of acetaldehyde in adequate amount can saturate both liver and endothelial aldehyde dehydrogenase (Hoover and Brien, 1981; Ward et al., 1997). In addition, the acetaldehyde doses used in our experimental protocol (10, 20 and 40 mg/kg) were in the range of those reported to induce conditioned

stimulus preference after systemic administration (Quertemont and De Witte, 2001), and conditioned place preference following intragastric administration (Peana et al., 2008). Thus, it seems reasonable to assume that under these circumstances acetaldehyde can cross the blood-brain barrier and act on the brain, although a direct measurement of brain acetaldehyde after peripheral administration is desperately needed.

Intragastric acetaldehyde administration (20 mg/kg) significantly enhanced dopamine overflow in the NAc; a quantitatively similar stimulation of dopamine overflow in the NAc by ethanol could only be observed using a dosage 50 times higher (1 g/kg i.g. vs 20 mg/kg i.g.) (Enrico et al., 2009; Melis et al., 2007). Similarly to data from ethanol, acetaldehyde administration at the lowest and the highest doses (10 and 40 mg/kg respectively) did not elicit any increase in dopamine extracellular levels in the NAc (Peana et al., 2008). Furthermore, in dopamine mesoaccumbens neurons, acetaldehyde administration using an exponentially increasing dosage paradigm, dose-dependently affected cell activity (Enrico et al., 2009; Foddai et al., 2004). In fact, while low doses of acetaldehyde (10 – 20 mg/kg i.v.) significantly increased neuronal activity (firing rate up to 184.6 ± 32.1% of basal values), any further increment in dosage (above 40 mg/kg) induced a decrease in all parameters studied (Melis et al., 2007; data for dosages above 40 mg/kg not shown). Indeed, a dose-related, biphasic effect of acetaldehyde has been described during acetaldehyde self-administration in the posterior VTA of alcohol-preferring rats (Rodd-Henricks et al., 2002), and during conditioned place preference in the rat following intragastric administration of acetaldehyde (Peana et al., 2008).

In line with our observations in dopamine mesoaccumbens neurons, intra-VTA administration of acetaldehyde via reverse dialysis was shown to increase dopamine output in the NAc of the rat in a dose-dependent fashion (Diana et al., 2008). These findings are particularly relevant when considered together with the available evidence of acetaldehyde self administration in the posterior VTA of alcohol-preferring rats (Rodd-Henricks et al., 2002), and the *in vitro* electrophysiological evidence of acetaldehyde -induced increase in firing of VTA neurons through action on two ionic currents: reduction of I_A and activation of I_h (Melis et al., 2007) (see next section on the effects of acetaldehyde *in vitro*).

In conclusion, our observations support a key role of acetaldehyde as a mediator of the mesolimbic dopamine stimulating effects following ethanol ingestion; this phenomenon might be related to ethanol's rewarding properties. Moreover, the effect of intragastric acetaldehyde administration on dopamine levels adds further support to the hypothesis that high blood acetaldehyde levels produced from peripheral metabolism of alcohol can saturate the blood-brain barrier and, cross into the brain, potentially adding to locally formed acetaldehyde produced from ethanol via the catalase-H_2O_2 system. Considering these data together, it is also tempting to speculate on a different role for acetaldehyde which is naturally contained in wine and other alcoholic beverages (Osborne et al., 2000; Peinado et al., 2004) as more than merely a volatile flavor compound (Genovese et al., 2005). In fact, acetaldehyde ingested together with alcoholic drinks may actually reach the central nervous system more efficiently, actively participating in the rewarding and motivational effects of ethanol.

Additional research in this direction is needed for a better understanding of the neurochemical substrates that mediate the expression of the conditioned rewarding properties of ethanol. Important insight, particularly for preventing relapse in alcoholics, may be provided by inhibition of the psychoactive properties of ethanol. In particular, although a specific neurobiological mechanism of action cannot be inferred from our data, it seems sensible to suggest that modulation of ethanol-derived acetaldehyde either by reducing its synthesis and/or by using sequestrating agents such as Dp, might exert a profound influence on the euphoriant effects of ethanol and its discriminative stimulus properties (Samson et al., 2004). Decreasing

the rewarding effects commonly associated with ethanol might lead to an alternative medical treatment of alcoholism.

Acetaldehyde in the VTA *in vitro*

In line with the *in vivo* reports on the effects of acetaldehyde on posterior VTA mentioned above (Foddai et al., 2004; Rodd-Henricks et al., 2002), *in vitro* electrophysiology of posterior VTA dopamine neurons also supports a crucial role played by acetaldehyde in alcohol-induced activation of midbrain dopamine cells (Melis et al., 2007). Indeed, ethanol-induced excitation of posterior VTA dopamine cells in a midbrain slice preparation appears to require ethanol's first metabolite (i.e. acetaldehyde), since an inhibitor of catalase is able to completely prevent ethanol's actions on VTA dopamine neuronal firing activity (Melis et al., 2007). It is important to stress that the above-mentioned study focuses on posterior VTA dopamine neurons, which have previously been shown to play not only a key role in alcohol rewarding and/or reinforcing actions *in vivo* (Rodd et al., 2004a; Rodd et al., 2005a; Rodd et al., 2005b; Rodd-Henricks et al., 2002), but also to be more sensitive to the rewarding properties of ethanol in those rat lines selectively bred for their alcohol preference (Rodd et al., 2004b; Rodd et al., 2007). Interestingly, it has been shown that the medial posterior VTA is a quadrant of this region with a substantial population of hyperpolarization activated inward current (i.e. I_h)-dopamine neurons (Margolis et al., 2008), primarily projecting to the NAc (Ford et al., 2006). It is, therefore, more likely that dopamine neurons located in this quadrant of the VTA form the mesolimbic dopamine system, which has long been implicated in reward-related learning, motivated behaviour and memory processes (for a review see (Alcaro et al., 2007). Given this key distinction, conflicting reports can be considered from a different point of view, especially given the thoroughly established heterogeneity of dopamine cell populations within the VTA (Ford et al., 2006; Lammel et al., 2008; Margolis et al., 2006a; Margolis et al., 2006b; Margolis et al., 2008; Wanat et al., 2008a).

Since, however, the hydrogen peroxide-catalase system is highly abundant in the VTA (Hung and Lee, 1998), we must consider the possibility that ethanol is oxidized in the VTA. Thus, the observation that when acetaldehyde formation is prevented, ethanol ceased to enhance the spike frequency of dopamine neurons, strongly suggests that acetaldehyde mediates ethanol-induced effects on dopamine neuronal spontaneous activity. In addition, the evidence that acetaldehyde *per se* produces a fast increase in dopamine neuronal firing activity, which is dose-dependent, and it occurs in a smaller dose range when compared to ethanol, substantiates this hypothesis (Diana et al., 2008; Melis et al., 2007). In particular, doses which produce a comparable effect on dopamine neuron firing rate are 100 mM and 10 nM for ethanol and acetaldehyde, respectively. Furthermore, an analysis aimed at determining which ionic conductances were affected by acetaldehyde has highlighted the role played by A-potassium channels (i.e. I_A), which control the spike frequency of dopamine cells by lengthening the interspike interval through a contribution to action potential generation (Hahn et al., 2003; Khaliq and Bean, 2008; Koyama and Appel, 2006; Yang et al., 2001). In addition, acetaldehyde also acts on I_h, which has been previously shown to be facilitated by ethanol (Brodie and Appel, 1998; Okamoto et al., 2006). Likewise, pharmacological blockade of these ion channels prevented acetaldehyde actions on dopamine neuronal firing activity, although at this stage actions of other ion channels accounting for the duration of the after-hyperpolarization period (i.e. AHP) cannot be ruled out. Interestingly, the stress-released peptide, corticotrophin-releasing factor (CRF), increases the spontaneous activity of VTA dopamine neurons through an enhancement of I_h in a mouse slice preparation (Wanat et al., 2008a), thus highlighting the molecular interplay between stress and dopamine and its related-behaviors.

Individual differences in dopamine neuron activity and effects of stress: future directions for understanding susceptibility to alcoholism?

Understanding the mechanisms of action of ethanol and acetaldehyde on dopamine neurons of the VTA may help us to understand the physiological alterations in these neurons that could participate in the development of alcohol addiction. In this context, it is also important to consider how stress exacerbates addictive states, how stress may modify dopaminergic neurotransmission, and how these stress-induced modifications may interact with ethanol. For example, stressful conditions, including drug-induced withdrawal, may change the phosphorylation states of different ion channels so that the cells are more or less responsive to ethanol or acetaldehyde. With a stress-induced reduction in inhibitory, barium-sensitive, inwardly rectifying potassium current, or a change in I_h, ethanol may more easily cause excitation of dopamine VTA neurons and this may be among the adaptations that link stress to alcoholism.

Studies on stress in rodent models have compared dopamine cell firing in control animals and in subjects that were exposed to different stressors, such as mild food restriction (chronic or acute)and brief cold swim. Mild chronic food restriction (maintaining animals at 90% of their body weight), acute food deprivation (2–24h), and brief cold swim (~5 min) have all been shown to increase the circulating levels of stress hormones (Dallman et al., 1999; Huber et al., 2001; Marinelli et al., 1996), and thereby represent good stress models. Studies using these paradigms have shown that a chronic food restriction increased the action potential output of dopamine cells from approximately 4 spikes/s to 6 spikes/s (Marinelli, 2007). With respect to acute stress, a short (16h) food deprivation period did not modify dopamine cell activity, but a longer (24h) deprivation produced an elevation of firing to approximately 5.7 spikes/s (Marinelli, 2007). Similarly, a brief (4–5min) exposure to cold swim also elevated firing rates of dopamine cells. This increase was measured 2h after exposure to the stress, it peaked at 24h, and it persisted for approximately 2 days (Marinelli, 2007). These studies indicate that both acute and chronic stress produce increases in dopamine cell firing.

Such increases in dopamine cell activity produced by stress have been shown to be paralleled by increases in drug self-administration. Thus, a mild reduction in food availability was shown to increase cocaine self-administration in the acquisition phase (Bongiovanni and See, 2008), the maintenance phase (Carroll, 1985; Carroll and Meisch, 1981), and in progressive ratio tests that estimate motivation to self-administer drugs (Rodefer and Carroll, 1996). Reduction in food availability also produced reinstatement of drug-seeking behavior (Shalev et al., 2003). Similar stressors were also shown to increase ethanol intake in outbred rat populations (Vengeliene et al., 2003), indicating that these effect can generalize to alcohol-seeking behavior. Additionally, a stressor as such as acute withdrawal from alcohol differently affects VTA dopamine neurons of C57 and DBA mice (Wanat et al., 2008b), which are known to self-administer and avoid alcohol, respectively. Remarkably, this type of stress is able to reverse the innate avoidance of DBA mice, which initiated to self-administer alcohol (Camarini and Hodge, 2004), thus highlighting how stress can change the behavioral responses to alcohol and, more generally, to abused drugs (Cabib et al., 2000).

In addition to the effects of stress to alter drug-seeking and alcohol-seeking behavior, there are individual differences that are not related to differences in stress conditions. Not all individuals respond in the same manner to drug exposure. Resistance and susceptibility to drugs of abuse varies greatly between individuals.

Humans show different reward sensitivities to addictive drugs (Abi-Dargham et al., 2003; De Wit et al., 1986), and similar profiles are observed in outbred populations of rats. For example, some rats show greater sensitivity to the rewarding properties of addictive drugs, whereas

others seem more resistant (Brodie and Appel, 2000; Grimm and See, 1997; Piazza et al., 1989; Piazza and Le Moal, 1998; Wanat et al., 2008b).

In addition, such individual differences in drug reactivity can be studied experimentally, in rodent lines that have been selectively bred for drug preference, or in animals that show a high locomotor response to a novel environment. Thus, high responders to novelty (HRs) are known to exhibit greater responding to psychostimulant drugs than low responders (LRs) (for review, see Marinelli, 2005) and greater ethanol intake in certain conditions (Cools and Gingras, 1998). In this model of enhanced addiction liability, the firing rate of dopamine cells, measured with *in vivo* extracellular recordings in anesthetized rats, was shown to be elevated in HR vs. LR rats (Marinelli and White, 2000). The firing frequency of dopamine cells in HR rats was 5.1 spikes/s whereas it was 4.1 spikes/s in LRs. In addition, the firing pattern of these cells was also different between groups. Dopamine cells show slow irregular firing with characteristic burst events (high-frequency clusters of spikes). In HR rats, burst events occurred every 1.3 sec, whereas they occurred only every 2.0 sec in LRs. Similar differences have been reported in rat strains that have been selectively bred for alcohol preference. Thus, Indiana alcohol-preferring P rats (Morzorati, 1998; Morzorati and Marunde, 2006) and Sardinian alcohol-preferring sP rats (Melis et al., 2009) show elevated firing rates of dopamine cells compared with their alcohol non-preferring counterparts both when recorded *in vitro*, and *in vivo* in anesthetized conditions. Interestingly, adolescent rats, which are also more susceptible to high alcohol intake (Vetter et al., 2007), exhibit elevated firing of dopamine neurons (McCutcheon and Marinelli, 2009).

In both stress models and individual differences models, elevated activity was shown to be accompanied by impaired ability of impulse-regulating autoreceptors to suppress dopamine neuron activity. Thus, administration of the dopamine D2-class autoreceptor agonist quinpirole suppressed dopamine firing to a less extent in HR rats than in LRs (Marinelli and White, 2000), as well as in stressed vs. control rats (Marinelli, 2007). Reduced ability of quinpirole to suppress firing activity in these models suggests that addiction-associated increases in dopamine cell activity could be the consequence of functional sub-sensitivity of dopamine D2-class autoreceptors. Interestingly, experimentally decreasing dopaminergic transmission (by administering the impulse-regulating autoreceptor agonist quinpirole) has been shown to decrease drug-seeking behavior (Marinelli et al., 2003)

Overall, these results highlight enhanced dopamine cell activity, whether spontaneously present or increased by stress is associated with enhanced drug self-administration and drug-seeking. On the other hand, low activity of the dopamine system is associated with low drug seeking and responding. These findings emphasize the role of dopamine cell activity as a possible key player mediating increased addiction liability and provide insight into understanding how environmental variables such as stress may increase addiction liability.

While it is only speculation at this point, differences in the reaction of the dopaminergic system to stress could underlie individual differences in the acute and chronic effects of ethanol and acetaldehyde. As described above, acute ethanol has actions on ion channels of DA VTA neurons, and chronic ethanol appears to produce long lasting changes in ion channel function. It remains to be seen whether stress produces either similar or complementary changes in ion channel function that can modulate ethanol action on DA VTA neurons. As posited above, a hypothetical stress-induced change in phosphorylation state of inhibitory, barium-sensitive, inwardly rectifying potassium current, or SK, M- or h-currents, could affect the response to ethanol. Individual differences in these stress-induced changes in ion channel function could result in different magnitudes of responses to acute or chronic ethanol. Ultimately, the interaction of stress and alcohol on neuronal function in the VTA could be an important factor in the development of alcoholism.

Conclusions

The findings reviewed above establish specific elements of ethanol action on dopamine VTA neurons. Both ethanol and acetaldehyde increase the spontaneous activity of dopamine VTA neurons, and at least some of the actions of ethanol may be produced by the formation of acetaldehyde from ethanol in the brain. As increases of dopamine neurotransmission are associated with the rewarding and reinforcing properties of drugs of abuse, these actions of ethanol and acetaldehyde may be critical for ethanol-seeking behavior. Stress also increases the spontaneous discharge of dopamine VTA neurons. Stress may act as a priming event, increasing dopamine activity altering the physiology of dopamine VTA neurons, and resulting in an increase in the likelihood of initiation of ethanol-seeking.

Understanding how acetaldehyde affects different ion channels active at subthreshold voltages and, therefore, elucidating its action on the characteristic pacemaker-like, single spike spontaneous activity of VTA dopamine neurons represents a future challenge which might have profound implications in the therapy of alcoholism.

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