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Effects of stress on dopamine neurons of the ventral tegmental area and interaction with drugs of abuse

Kelly Conrad, Charles Rudick, Donald Cooper, Francis White, and Michela Marinelli, Dept. Cellular & Molecular Pharmacology, Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA

Resistance and susceptibility to drugs of abuse is greatly influenced by environmental variables, such as exposure to stress. In this set of studies we examined how stress may favor addiction liability by inducing plasticity of midbrain dopamine neurons, one of the major neuronal substrates of addiction. The activity of midbrain dopamine neurons was assessed with in vivo extracellular recordings. Male rats were compared in basal conditions (control) and after exposure to different stressors: mild food restriction (acute or chronic), and brief cold swim. Addiction liability was evaluated with cocaine self-administration paradigms. Acute and chronic stress produced a marked increase in dopamine cell firing. This increase was observed in the presence of the stress and persisted for approximately 2 days after its termination. Stress also changed the firing pattern of dopamine cells, by increasing clusters of high-frequency spikes (bursting activity). These effects were accompanied by impaired ability of impulse-regulating autoreceptors to suppress dopamine neuron activity, suggesting that functional sub-sensitivity of these receptors may underlie these effects. In parallel, stress modified reactivity to cocaine by increasing drug self-administration and drug-seeking. Again, these effects were observed in the presence of the stress, and lasted approximately 2 days after its termination. Finally, experimentally decreasing dopaminergic transmission (by administering an impulse-regulating autoreceptor agonist) decreased drug-seeking behavior. These results suggest that stress can boost dopaminergic transmission to enhance drug self-administration and drug-seeking. These findings provide insight into understanding how environmental variables such as stress produce plasticity of dopamine neurons that could facilitate addiction liability.

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Effects of ethanol on neurons of the VTA *in vitro*: Mechanisms and stress

Mark S. Brodie, Department of Physiology and Biophysics, University of Illinois at Chicago, Chicago, IL, USA

The ventral tegmental area (VTA) is a critical component of brain reward systems. In dopaminergic (DA) neurons of the VTA of rats and mice, studied in vitro and in vivo, ethanol excites DA VTA neurons. This excitation is blocked by quinidine, which blocks some potassium channels, and is partly mediated by M-current. DA VTA neurons possess a cationic current (I_h) which is blocked by ZD7288. We demonstrated that I_h is increased in DA VTA neurons of rats by ethanol. ZD7288 does not decrease ethanol excitation in rats. Okamoto et al (2006) demonstrated that ZD7288 decreases the firing rate and reduces ethanol excitation in DA VTA neurons of mice. In our more recent investigations, we have observed that blockade of I_h in mice results in the exposure of a previously unknown action of ethanol to increase G-protein linked inwardly rectifying potassium (GIRK) channel activity in DA VTA neurons, which is an inhibitory effect which counteracts the ethanol excitation of DA-VTA neurons. This effect of ethanol on GIRKs in the presence of ZD7288 is only seen in rats at very high ethanol concentrations. Other ion channels in the membrane of DA VTA neurons also can alter the potency of ethanol to excite DA VTA neurons. This interplay of ion channel activity and ethanol action may have significant implications in physiological situations, such as those induced by stress, and plasticity of ion channel activity is likely a critical factor in the aspects of alcohol addiction related to the VTA.

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D-Penicillamine prevents ethanol and acetaldehyde-induced increase in mesolimbic dopamine transmission

M. Diana, A. Lintas, D. Sirca, M. Mereu, A. Golosio, P. Enrico, "G. Minardi" Cogn. Neurosci. Lab., Dept. of Drug Sci., Univ. of Sassari, Italy

Acetaldehyde (ACD) is the main metabolite of ethanol (EtOH); recent evidence suggests that ACD may significantly contribute to EtOH rewarding properties . Previous research in our laboratory has shown that ACD stimulates ventral tegmental area (VTA) dopaminergic neurons activity and that pretreatment with 4-methyl-pyrazole (4MP, an inhibitor of alcohol-dehydrogenase), prevents EtOH-induced increase in neuronal firing leaving ACD-induced effects unmodified. To further characterize the contribution of ACD to the stimulating properties of EtOH, we studied the effects of ACD and EtOH on VTA dopaminergic cells using single unit extracellular recordings coupled with antidromic identification from the NAcb and by microdialysis . Administration of ACD (5-20 mg/kg i.v.) dose-dependently increased the firing rate, spikes/burst, and burst firing of VTA neurons. EtOH (250-1000 mg/kg i.v.) administration produced similar increments in the same electrophysiological parameters. In animals pretreated with D-Penicillamine (50 mg/kg intraperitoneal, 30' before drug challenge), EtOH (250- 1000 mg/kg i.v.) and ACD (5-20 mg/kg i.v.) effects on the firing rate, spikes/burst, and burst firing were drastically reduced. Further, we used in vivo microdialysis to measure dopamine (DA) output in the Nucleus Accumbens shell (Nacbs) of male albino Wistar rats in response to a challenge with ACD and EtOH. Both EtOH (0.5, 1.0, 2.0 g/kg) and ACD (10, 20, mg/kg) were administered by gavage. To evaluate the role of VTA, ACD (50, 75, 100 μM) was administered via reverse dialysis within the VTA while measuring DA output in the Nacbs. Intragastric EtOH and ACD administration dose-dependently increased DA extracellular levels in the Nacbs; similar results were obtained with intra-VTA ACD administration. These findings support the hypothesis that ACD stimulates mesolimbic DAergic neurons by an intra-VTA mechanism, thereby contributing to the EtOH-induced increment in DA outflow in the NAcbs. These observations add further evidence to the idea that EtOH increases activity of Nacb-projecting VTA dopaminergic neurons via ACDl and may bear important theoretical consequences on pharmacological therapies of alcohol abuse and alcoholism.

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Acetaldehyde in the ventral tegmental area is essential for alcohol activation of mesolimbic dopamine neurons

Miriam Melis and Marco Diana, Centre of Excellence on "Neurobiology of Addiction" and "B.B. Brodie" Dept. of Neuroscience, University of Cagliari, Monserrato, and "G. Minardi" Cogn. Neurosci. Lab., Dept. of Drug Sci., Univ. of Sassari, Italy

Alcoholism is a major addictive disorder affecting society and individuals. Many complex neurobiological mechanisms are thought to be at the basis of this brain disease, and have been extensively investigated in the past decades. Recently, one of the main mechanisms underlying alcohol rewarding properties has been found to be the activation of the mesolimbic dopamine system after acute administration. However, evidence that in vitro alcohol first metabolite acetaldehyde accounts for alcohol-induced excitation of mesolimbic dopamine neurons will be presented. In fact, when alcohol oxidation is prevented in the ventral tegmental area (VTA) alcohol ceases to increase dopamine neuronal firing. Thus, acetaldehyde formation in the VTA appears as a key mechanism for alcohol-induced activation of dopamine neurons. Additionally, acetaldehyde per se enhances dopamine neuronal activity in a dose-dependent fashion. Furthermore, acetaldehyde-induced enhancement of dopamine neuronal firing involves reduction of IA and activation of Ih. These results provide in vitro evidence for a key role of acetaldehyde in alcohol activation of mesolimbic dopamine system. Additionally, these findings might explain why acetaldehyde has been shown to be not only rewarding by itself, but also necessary for affective/motivational properties of alcohol. Finally, these results might prove useful in devising new therapeutic strategies to treat alcoholism.