ETHANOL-INDUCED MODULATION OF DOPAMINE TRANSMISSION AND SYNAPTIC ACTIVITY IN STRIATAL SUBREGIONS

– focus on inhibitory receptors

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– focus on inhibitory receptors
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ABSTRACT

Background: Alcoholism is a chronic brain disease, affecting neurocircuitries involved in reward and learning. The rewarding effects of alcohol (ethanol) are believed to result from increased dopamine levels in the nucleus accumbens (nAc) via the mesolimbic system. The exact mechanisms through which this occurs are debated, but evidence from the current research group suggests that ethanol activates the mesolimbic system via a reciprocal connection between the nAc and the ventral tegmental area (VTA), involving the activation of glycine receptors (GlyRs) in the nAc. Research from other groups suggests that ethanol may activate the mesolimbic system via its primary metabolite, acetaldehyde, through direct actions in the VTA. The effects of acetaldehyde in the nAc-VTA-nAc neuronal circuitry however, have not been investigated. Dopamine signaling is also important in the dorsolateral striatum (DLS), an area involved in habit formation. The effects of ethanol on dopamine levels in this region are poorly understood, as are the roles of inhibitory GlyRs and γ-aminobutyric acid type A (GABA_A) receptors, in mediating these effects. Aims: To explore the effects of ethanol (or acetaldehyde) on dopamine transmission and synaptic activity in the nAc and DLS. Special emphasis is placed on the involvement of GlyRs and GABA_A receptors. Methods: Dopamine transmission was studied using in vivo microdialysis in awake, adult Wistar rats. This method was also used for local administration of relevant drugs/substances. Synaptic activity was measured by in vitro field-potential recordings in coronal brain slices from juvenile and adult Wistar rats. All animals were alcohol-naïve. Results: Local acetaldehyde administration did not increase nAc dopamine levels, nor did sequestering of ethanol-derived acetaldehyde affect the dopamine-elevating properties of ethanol. Results also showed that the dopamine-enhancing effects of ethanol were mediated by GlyRs in the nAc, but neither by GlyRs nor GABA_A receptors in the DLS. Ethanol produced both enhancing and depressing effects on synaptic activity, which were dependent on the region studied, the age of the animal, as well as the concentration applied. The relative involvement of inhibitory receptors also differed in an age and region-specific manner. Conclusions: The results in this thesis indicate that acetaldehyde is not involved in the dopamine-enhancing effects of ethanol that are mediated via the reciprocal nAc-VTA-nAc neuronal circuitry. Furthermore, it is shown that changes in dopamine and synaptic activity induced by acute ethanol administration are modulated by inhibitory receptors in a region and age-specific manner. By pinpointing similarities and differences in response to alcohol between reward-related and habit-related parts of the brain this research may contribute to furthering the knowledge of how alcohol addiction develops and progresses.

Key words: Dopamine, ethanol, acetaldehyde, striatum, glycine receptor, GABA_A receptor