Pharmacological and Chemogenetic Manipulation of Norepinephrine and the Locus Coeruleus System in Rats Alters Performance in an Auditory Detection Task

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Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental spectrum disorder categorized by inattention, hyperactivity, and impulsivity with unclear neurobiological etiology. Common treatments include methylphenidate (MPH) and clonidine (CLON), which modulate norepinephrine (NE) signaling in the brain by increasing or decreasing levels respectively. While norepinephrine is strongly implicated in ADHD treatment, the underlying neural mechanisms are not well understood. One possible site of action is the locus coeruleus (LC), a noradrenergic brain region which regulates attention and behavioral responses to environmental changes; LC dysregulation has been heavily implicated in ADHD. Our lab recently found that LC hyperactivity produces an ADHD-like phenotype in rats, which is reversed by MPH, and proposed that reducing baseline LC-NE activity may be central to the clinical efficacy of pharmacotherapies such as CLON and MPH. The purpose of this experiment was to identify the influence of norepinephrine, and specifically the locus coeruleus/norepinephrine pathway, in altering decision-making phenotypes characteristic of ADHD in a rat auditory detection task. Rats were trained to perform an operant discrimination between two tones for water reinforcement; this requires sustained attention and response inhibition, two behaviors disrupted by ADHD. To examine the role of ADHD pharmacotherapies in this task, rats received injections of clonidine, an alpha-2 receptor antagonist that decreases cortical NE levels prior to testing. To examine the specific role of LC-NE, we expressed hM4Di (a modified human M4 muscarinic receptor) or GFP in LC using a dual CRE-recombinase and virus technique. LC-hM4Di is activated by clozapine N-oxide (CNO), selectively inhibiting norepinephrine pathways originating from the LC by hyperpolarizing neurons. We calculated hit, false alarm, miss, and correct rejection rates as well as d' and β. D' is an indicator of the certainty of a decision and β is the sensitivity value of a stimulus being the target, according to the signal detection theory. We found that clonidine decreased hit rates and false alarm rates overall but produced performance-enhancing effects on task performance at low doses (increased d'); meanwhile high doses of clonidine impaired task performance (decreasing hit rate and d'). This is consistent with clonidine's clinical use as an ADHD treatment at normal concentrations and its sedating effects at higher concentrations. Interestingly, CNO enhanced task performance in a dose-dependent fashion (false alarms decreased, d' increased), suggesting that the cognitive enhancing effects of low-dose clonidine may be due to its effects on the LC, while its impairing effects at high doses are due to action at other sites. These findings will contribute to a greater understanding of how the actions of clonidine on LC-NE produce therapeutic effects and increase potential for development of more safe, effective, and targeted treatments of ADHD. Supported by NIH R25ES020721, F31DA047068, and R01DA006214 and ORED.