Neural Substrates of Stress-effects on Performance: Pharmacological Countermeasures

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Future space missions will require astronauts to live and work in space for prolonged periods of time, performing highly technical tasks while persistently enduring the environmental, cognitive, and physiological stresses associated with long-duration space flight. To ensure the success of these missions, it will be necessary to understand the impact of acute and chronic stress on neurobehavioral function and cognitive performance so that appropriate countermeasures can be developed to sustain high levels of functioning during extended stays in space.

The ability to sustain attention is critical to the successful performance of complex tasks over extended periods of time. We developed a target detection continuous performance task that rats can learn rapidly. Rats initiate each trial by pressing one lever, and then must discriminate between two signal lights to determine if the one illuminated is a target or non-target. If the target signal light is illuminated the rat must press a second lever to obtain food reward. If the non-target is illuminated he must withhold responding with no reward and await the next trial. Targets occur randomly on 20% of the trials. This task is the means by which we measure performance abilities and changes therein induced by stress and pharmacologic treatments.

Effects of stress on performance in the target detection task. Acute white noise stress at 90 db significantly increased responding to the non-target stimulus (false alarm (FA) errors) in this task. Interestingly, this effect habituated rapidly, so that subsequent administration of 105 db did not influence performance. A combined noise+restraint stress appeared to more effective in disturbing task performance. Interestingly, some animals showed a much larger effect of this stressor than others. The alpha2 adrenoceptor agonist clonidine (which decreases LC-NE neurotransmission) at 8 ug/kg reduced the FA error rate seen with 90 db noise stress. Higher doses of clonidine (25 ug/kg) produced sedation. These preliminary experiments require confirmation with additional studies, but they suggest that the norepinephrine (NE) brain system may be involved in stress effects on performance in this task.

Effects of idazoxan on performance in the target detection task. The alpha2 adrenoceptor antagonist idazoxan increases firing of locus coeruleus (LC) NE brain neurons and release of NE from LC terminals. Our view of LC’s role in performance predicts that this agent should worsen performance on this task, with increased FA errors. Systemic idazoxan had no effect on rats that were performing marginally in the task (i.e. a 30% false alarm rate). However, this compound markedly increased false alarms in rats that had low baseline false alarm rates in the absence of the drug. These preliminary results are consistent with the view that moderate levels of tonic LC activity are critical for maintaining focused attentiveness to task stimuli and performing optimally, and that behavioral performance declines when tonic LC firing rates are increased. Thus, the poor performance of some rats pre-drug may have been due to a high level of baseline tonic LC activity, placing them at the right of the inverted U relationship. This pre-existing heightened LC activity could have created a ceiling effect that prevented idazoxan from further increasing LC firing rates and disrupting responses. These effects of idazoxan for some but not all rats are consistent with those above for effects of noise+restraint stress on performance in only a subpopulation of animals. Additional studies are underway to investigate these individual differences in the vulnerability to stress effects on performance, and to examine specific countermeasures for these individuals.

Role of the LC in circadian regulation of sleep and waking. We implemented a telemetry system for recording EEG, EMG, body temperature and locomotor activity in freely moving, untethered rats. This system produces robust sleep measures over long periods of time. We also developed a mechanism for producing sleep deprivation, consisting of a slowly rotating wheel that the rat is within. This device allows access to food and water and also contains levers and stimuli to allow task performance during the sleep deprivation period. We will use this system to deprive rats of sleep at different times of their circadian rhythm and examine effects on performance. We will then analyze effects of manipulating the LC system on the performance deficits produced by sleep deprivation.

Impact of these findings. The development of a target detection task for the rat now allows us to test the effects of stressors on a type of performance important in space missions. This model will also allow analysis of manipulations of the brain NE system of the LC in these stress effects to facilitate development of countermeasures to stress effects. We found that acute stress increases FA errors in this task, and that decreasing neurotransmission in the LC system with clonidine may offset this effect. Accordingly, we also found that increased NE neurotransmission (with idazoxan) in non-stressed animals worsens performance on this task by producing FA errors. These results indicate that the LC-NE system may be a valid target for development of countermeasures to the effects of stress on performance.