

For the month of April, we are highlighting a research article that discusses the role of reward and aversion in drug taking behavior. Such a perspective requires an understanding of animal models of both the rewarding and aversive effects of drugs and how the two affective properties measured by each interact to impact drug taking. The article is by Contreras et al. entitled "Interaction of the interoceptive insula disrupts drug craving and malaise induced by lithium," published in the journal *Science* 318: 2007; 655-658.

Following up the exciting report by Naqvi et al. (*Science* 315:2007; 531-534) that insular cortex damage in humans disrupted nicotine craving, Contreras et al. (2007) explored the role of the insular cortex in "homeostatic and emotional information that are important elements in motivational decisions." Specifically, they were interested in the effects of insular inactivation on the rewarding properties of amphetamine (as measured in the conditioned place preference design) and the aversive (sickness) inducing properties of the emetic LiCl.

In relation to amphetamine reward, the authors first established a conditioned place preference in rats by pairing amphetamine with the normally nonpreferred side of a two compartment place preference chamber. As expected, animals with such a conditioning history acquired the place preference. Once established, the animals were injected bilaterally with lidocaine into the insular cortex. Animals treated this way no longer displayed the amphetamine-induced place preference. Interestingly, the preference returned when the animals were tested several days later (after the dissipation of the lidocaine). These effects were not accompanied by changes in locomotor behavior, but were by c-Fos activation in the insular cortex (but not in the adjacent primary somatosensory area). These results clearly implicated the insular cortex in the rewarding effects of amphetamine and suggested that this area of the brain monitors and reports this affective component.

In a parallel study, Contreras et al. (2007) subjected rats to an injection of LiCl and assessed several indices of malaise, e.g., latency to lie on belly and time spent in this position. As expected, the emetic affected these behaviors (reduced latency and increased time). Interestingly, inactivation of the insular cortex by lidocaine delayed the onset of nausea related behaviors for a duration that approximated lidocaine's time course of effectiveness. This result demonstrated that, similar to the development of place preferences with amphetamine, the insular cortex was necessary for the expression, and possibly the sensation, of drug-induced nausea. Furthermore, as with the expression of place preferences with

amphetamine, malaise induced by LiCl also resulted in c-Fos activation in the insular cortex, specifically in the primary interoceptive cortex (located in the posterior granular insular cortex; an area associated with disgust and nausea in humans). Although not reported in this paper, lesions of the insular cortex do disrupt taste aversion learning, an effect consistent with the effects of its inactivation on malaise.

These two affective states, i.e., reward and aversion (or sickness), may play roles in drug taking behavior. The case for reward is quite easy to make. It is one often discussed for drug taking behavior, i.e., the rewarding effects of a drug are instrumental in the initiation of drug use. The maintenance of drug use (and its escalation) may be more dependent on processes other than (or in addition to) reward (for a review see Koob and LeMoal, 2008). As described by Contreras et al. (2007), drug craving may be mediated by the “negative affect symptoms of drug use, including anxiety, irritation and sadness.” Indeed, it would be interesting to see if temporary inactivation of the insular cortex can block aversions to contexts associated with drug withdrawal. Assessments along these lines will clarify the role of negative affect in drug taking - either in its initiation (as a protectant factor) or in its maintenance and escalation (via negative reinforcement).

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