History Impacts the Aversive Effects of Drugs

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Background: Previous exposure to certain drugs can enhance sensitivity to reinforcing effects, facilitating self-administration in nonhumans and likely impacting vulnerability to abuse drugs in humans. In addition to reinforcing effects drugs can also have aversive effects that might modulate abuse-related effects. Initiation and maintenance of drug use as well as relapse have been hypothesized to be associated with sensitivity to aversive effects. This study compared sensitivity to the kappa opioid receptor agonist spiradoline in rats with and without prior exposure to histamine to test the hypothesis that a history with one aversive drug might impair or facilitate the aversive effects of a second drug.

Methods: Male Sprague-Dawley rats with intravenous (i.v.) catheters chose (100 trials/session) between a pellet alone and a pellet + an infusion. All rats were first tested with saline. Thereafter, half of the rats (8) were tested with histamine followed by spiradoline while the other half (8) were tested with spiradoline followed by histamine.

Results: When choosing between a pellet and a pellet + saline, rats responded on each lever (indifference) and completed all trials. The rats that were tested first with histamine predominantly chose the pellet alone (>80%), avoiding the pellet + histamine. Rats that received histamine first also avoided the pellet + spiradoline, instead choosing the pellet alone (>70%). The rats that were tested first with spiradoline responded approximately equally on each lever, receiving spiradoline in doses sufficient to significantly decrease the number of trials completed; however, rats that were tested first with spiradoline avoided a pellet + histamine, choosing the pellet alone (>75%).

Conclusions: This study shows that aversive effects of spiradoline are evident only after a history with histamine. Histamine is a more effective aversive stimulus in naïve rats perhaps due to its very rapid onset and offset of action compared with spiradoline. This study suggests that avoidance of drug effects can be a learned behavior that generalizes to different drug classes when the aversive consequences are discrete. Experience with aversive effects might also impact reinforcing effects of different drugs, with diminished sensitivity to aversive effects predicting vulnerability to drug abuse.