A Selective Role for Dopamine D_4 Receptors in Modulating Reward Expectancy in a Rodent Slot Machine Task

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Background: Cognitive distortions regarding gambling outcomes confer vulnerability to pathological gambling. Using a rat slot machine task (rSMT), we previously demonstrated that the nonspecific D_2 agonist quinpirole enhances erroneous expectations of reward on near-miss trials, suggesting a pivotal role for the D_2 receptor family in mediating the near-miss effect. Identifying which receptor subtype is involved could facilitate treatment development for compulsive slot machine play.

Methods: Thirty-two male Long Evans rats learned the rSMT. Three flashing lights could be set to on or off. A win was signaled if all three lights were set to on, whereas any other light pattern indicated a loss. Rats then chose between responding on the collect lever, which delivered 10 sugar pellets on win trials but a 10-second time penalty on loss trials, or to start a new trial instead. Performance was assessed following systemic administration of selective D_2, D_3, and D_4 receptor ligands.

Results: The selective D_2 antagonist L-741,626, the D_3 antagonist SB-277011-A, and the D_3 agonist PD128,907 had no effect. In contrast, the selective D_4 agonist PD168077 partially mimicked quinpirole's effects, increasing erroneous collect responses on nonwin trials, whereas the D_4 antagonist L-745,870 improved the error rate. L-745,870 was also the only antagonist that could attenuate the deleterious effects of quinpirole.

Conclusions: The dopamine D_4 receptor is critically involved in signaling reward expectancy in the rSMT. The ability of L-745,870 to reduce the classification of losses as wins suggests that D_4 antagonists could be effective in treating problematic slot machine play.

Key Words: Anterior cingulate, gambling, incentive salience, L-745,870, near-miss, quinpirole

Cognitive theories suggest that the transition from recreational to problem gambling may depend on an individual's vulnerability to cognitive biases regarding decision making under uncertainty (1,2). One such cognitive distortion is the near-miss effect. Near-misses are unsuccessful outcomes that are structurally proximal to a win that generate the sensation of almost winning (3). While subjectively aversive, near-misses generate beliefs of mastery and galvanize further game play (3,4).

Using a rodent slot machine task (rSMT), we reported that rats are also susceptible to putative win signals in nonwinning trials, akin to a near-miss effect (5). In addition, the erroneous expectation of reward following such a loss increased after administration of the dopamine (DA) D_2-like receptor agonist quinpirole (5). Numerous studies suggest an important role for the D_2 receptor family in determining vulnerability to dependency (6–8). Furthermore, this receptor class plays a pivotal role in the incentive salience theory of addiction, which proposes that environmental stimuli previously paired with drugs or rewards can develop considerable influence over behavior (9–11). Given that the near-miss effect could arguably reflect the misattribution of incentive salience to a seemingly reward-related stimulus, it is perhaps unsurprising that a D_2-like receptor agonist increased the misinterpretation of near-misses as wins in our rodent model.

However, it is unclear which D_2 receptor subtype was critically involved in enhancing the erroneous expectation of reward in the rSMT. The majority of studies targeting D_2-like receptors often attribute their findings to the D_2 receptor itself, potentially due to its relative abundance within the D_2 family (12) and localization within reward-related neural structures such as the dorsal striatum and nucleus accumbens (13). However, the D_2 receptor class also contains D_3 and D_4 receptors, both of which are affected by drugs such as quinpirole (14,15), and may play an important role in addictive and impulsive behaviors. D_3 receptors are co-localized with D_2 receptors in limbic areas critical for the reinforcing properties of addictive drugs (16), leading to speculation that D_3 antagonism may be a promising treatment for addiction (17,18). Indeed, D_3 antagonists can attenuate cocaine- and nicotine-induced conditioned place preference in rats (18,19) and reduce drug-seeking behaviors (19–21). Given that the effects of D_3 antagonists are most pronounced when drug self-administration depends on conditioned cues, it has been postulated that D_3 receptors play an important role in the attribution of incentive salience (18,21,22) and thus may contribute to the near-miss effect.

In contrast, D_4 receptors are primarily located within frontal cortical regions (23) and consequently represent a potential target for modulating higher order cognitive processes (24). D_4 receptor polymorphisms are associated with a wide range of psychiatric disorders that have impulsivity or thought disturbances as a key component, such as schizophrenia, attention-deficit/hyperactivity disorder, substance abuse, and pathological gambling (25–28). However, clinical trials of selective D_4 agents as

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neuroleptics have not been encouraging (28,29), and animal studies investigating the behavioral effects of D_4 receptor manipulations have yielded mixed results (30,31). Still, evidence is emerging to suggest that D_4 receptors play a critical role in attributing emotional salience to environmental stimuli and guiding response to these cues (32–34). The following pharmacologic experiments using the rSMT were therefore performed to determine whether D_2, D_3, or D_4 receptors are critically involved in the near-miss effect.

Methods and Materials

Subjects

Subjects were 32 male Long Evans rats (Charles River Laboratories, St. Constant, Canada) weighing 275 g to 300 g at the start of testing. Subjects were food-restricted to 85% of their free-feeding weight and maintained on 14 g rat chow daily. Water was available ad libitum. All animals were pair-housed in a climate-controlled colony room maintained at 21°C on a reverse 12-hour light-dark schedule (lights off 8:00 AM). Testing and housing were in accordance with the Canadian Council of Animal Care and all experimental protocols were approved by the Animal Care Committee of the University of British Columbia.

Rodent Slot Machine Task

Testing took place in eight standard five-hole operant chambers, each enclosed within a ventilated sound-attenuating cabinet (Med Associates Inc, St. Albans, Vermont). A full description of the behavioral apparatus, habituation, and training can be found in our previous publication (5) and in the Supplemental Methods in Supplement 1. A diagram illustrating the different stages of each trial is shown in Figure 1. In brief, rats responded to a series of three flashing lights, analogous to the three wheels of a slot machine, which caused the lights to set to on or off. A win (i.e., reward available) was signaled by all three lights setting to on, whereas any other light pattern indicated a loss. At the end of the trial, rats chose between responding on the left (collect) lever, which resulted in 10 sugar pellets on win trials but a 10-second time penalty on loss trials, or starting a new trial instead by responding on the right (roll) lever. Hence, the optimal strategy was to choose the collect lever on win trials and the roll lever on all other trial types.

The use of three active holes resulted in eight possible trial types ([1,1,1]; [1,1,0]; [1,0,1]; [0,1,1]; [1,0,0]; [0,1,0]; [0,0,1]; [0,0,0]). The incidence of the different trial types was distributed evenly throughout the session such that each trial type occurred at least once every 8 trials and not more than twice in every 16 trials. The exact sequence of trials was randomized within these constraints. Animals received 5 daily testing sessions per week until statistically stable patterns of choice had been established over 5 sessions across the different trial types (84 sessions total). All sessions lasted for 30 minutes and animals could complete an unlimited amount of trials within this time.

Pharmacologic Challenges

Details of suppliers and formulation can be found in the Supplemental Methods in Supplement 1, plus the affinities each compound exhibits for different receptor subtypes (Table S4 in Supplement 1). Once stable baseline behavior had been established, rats were separated into two cohorts matched for task performance. The effects of the following compounds were assessed in group 1: the selective D_2 receptor antagonist

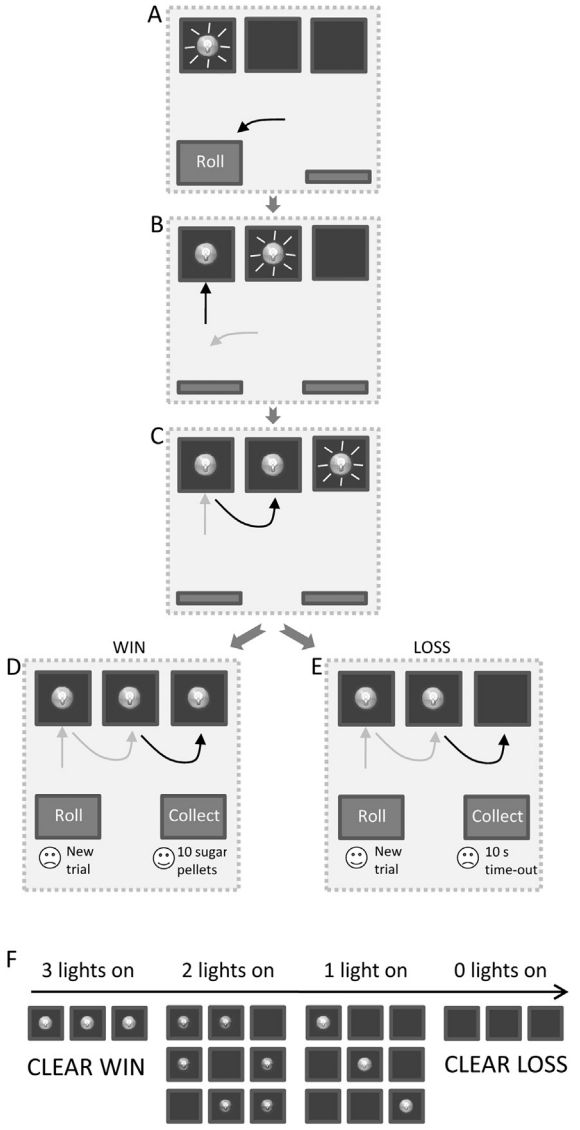

Figure 1. Trial structure of the rat slot machine task. **(A)** Animals initiated each trial by responding on the roll lever. This lever retracted and the light inside hole 2 began to flash. Once the rat responded at this aperture, the light inside set to on or off for the remainder of the trial and either a 20 kHz (light on) or 12 kHz (light off) tone sounded for 1 second, after which the light in hole 3 began to flash. **(B)** Again, a nosepoke response resulted in the light setting to on or off and the sounding of the 20 kHz/12 kHz tone, after which the light in hole 4 started to flash. **(C)** Once the rat responded in hole 4 and the light inside set to on or off, again accompanied by the relevant tone, both the collect and roll levers were presented. The rat was then required to respond on one of the levers; the optimum choice was determined by the pattern of lights in holes 2 to 4. **(D)** On win trials, all three lights were set to on (1,1,1), and a response on the collect lever led to delivery of 10 sugar pellets. **(E)** If any of the lights were set to off (i.e., a loss trial), a response on the collect lever led to a 10-second time-out period, during which reward could not be earned. If the rat chose the roll lever on any trial type, then the collect lever retracted, the potential reward or time-out was cancelled, and a new trial began. Hence, on win trials, the optimal strategy was to respond on the collect lever to obtain the scheduled reward, whereas on loss trials, the optimal strategy was to instead respond on the collect lever and start a new trial. If the rat chose to collect, both the collect and roll levers retracted until the end of the reward delivery/time-out period, after which the roll lever was presented and the rat could initiate the next trial. **(F)** There were eight possible trial types. (Modified with permission from Winstanley *et al.* [5]).