Sex differences in dopaminergic regulation of risky decision making

The University of Texas at Austin
Waggoner Center for Alcohol & Addiction Research

Leah Truckenbrod[1], Alexa-Rae Wheeler[1], Emily Cooper[2], Caitlin A. Orsini[1,2,3,4]

[1]Department of Neuroscience, [2]Department of Neurology, [3]Department of Psychology, [4]Waggoner Center for Alcohol and Addiction Research
University of Texas at Austin

Background

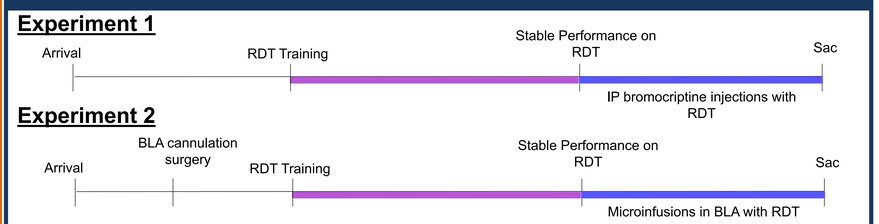
- The ability to make decisions and evaluate the subsequent risk is necessary to navigate everyday circumstances. Various psychiatric conditions, such as substance use disorders, however, are characterized by impairments in the ability to make such decisions.
- Dopamine (DA) transmission within corticolimbic-striatal circuitry, specifically within the basolateral amygdala (BLA), is integral in modulating decisions involving reward uncertainty.
- Although DA receptors mediate punishment-related decision making in the striatum, their role in the BLA is unknown.

Do dopamine receptors in the BLA contribute to decision making involving risk of explicit punishment?

- Females are more risk averse than males and are more sensitive to dopaminergic manipulations of punishment-based decision making.
- Activity in the BLA, either at baseline or in response to an aversive stimulus, is greater in females than males.
- There is greater D2 dopamine receptor (D2R) mRNA in the BLA of females compared to males.

Do differences in sensitivity of DA receptors in the BLA contribute to sex differences in decision making involving risk of explicit punishment?

Methods



Experiment A: The objective of Experiment 1 was to determine the behavioral effects of systemic administration of a D2R agonist, bromocriptine, on RDT performance. Male (n = 8) and female (n = 8) Long Evans rats were food restricted and trained in the Risky Decision-making Task (RDT; Figure 1) until stable behavior emerged. Using a within-subjects design, rats were then given intraperitoneal (IP) injections of bromocriptine (0.0, 1.0, 3.0, 5.0 mg/kg) 40 min prior to RDT testing.

Experiment B: The objective of Experiment 2 was to determine the behavioral effects of intra-BLA microinfusions of a D2R agonist, quinpirole, or antagonist, eticlopride, on RDT performance. Male (n = 8) and female (n = 6) rats were implanted with bilateral cannulae targeting the BLA (AP: -3.3, ML: ±4.9, DV: -7.5). After one week of recovery, rats were food restricted and trained in the RDT until stable behavior emerged. Using a within-subjects design, rats received microinfusions (0.5 µl/hemisphere at a rate of 0.5 µl/75 s) of quinpirole (0.0, 1.0, 10.0 µg) or eticlopride (0.0, 0.1, 1.0 µg) into the BLA 10 min prior to RDT testing.

Behavioral Testing: Figure 1 depicts a single trial in the Risky Decision-making Task (RDT). Each trial begins with illumination of the house light and trough light. Upon nosepoking into the trough, the levers extend into the operant chamber. A lever press on the small, "safe" lever results in delivery of a single food pellet whereas a lever press on the large, "risky" lever results in the delivery of two food pellets, accompanied by an increasing probability of mild foot shock across trial blocks (0%, 25%, 50%, 75% and 100%, respectively). Each of the 5 blocks of trials begins with 8 forced choice trials in which the shock contingencies in effect for that block are established (4 presentations of each lever alone, randomly presented), and are followed by 10 free choice trials, for a total of 90 trials across 5 blocks in 60 minutes.

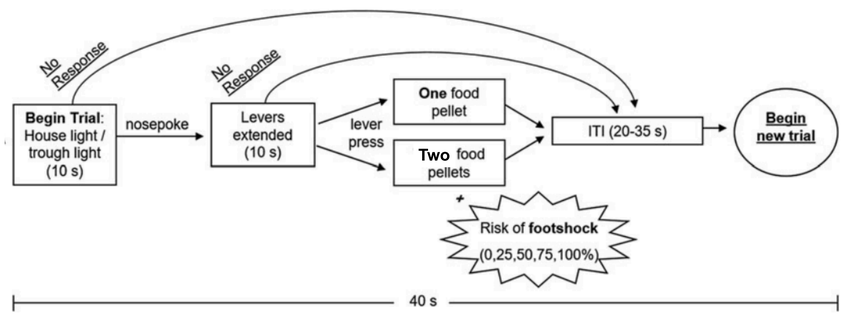


Figure 1: Schematic of the Risky Decision-Making Task (RDT). Adapted from Orsini et al. (2019) *Methods Mol Biol.*

Systemic administration of a D2R agonist decreases risk taking

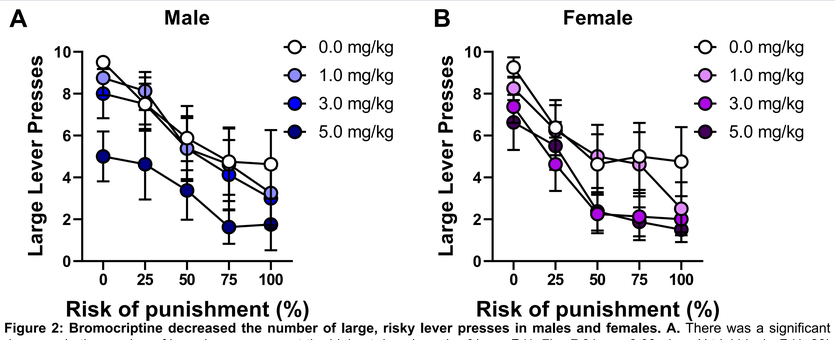


Figure 2: Bromocriptine decreased the number of large, risky lever presses in males and females. A. There was a significant decrease in the number of large lever presses at the highest dose in males [dose, F (1, 7) = 7.01, p = 0.03; dose X trial block, F (4, 28) = 0.49, p = 0.74]. **B.** Both the medium and high dose of bromocriptine caused a significant decrease in the number of large lever presses in females [medium: dose, F (1, 7) = 8.43, p = 0.02, dose X trial block, F (4, 28) = 0.25, p = 0.91; high: dose, F (1, 7) = 5.67, p = 0.05, dose X trial block, F (4, 28) = 0.72, p = 0.58].

Intra-BLA D2R agonist decreases risk taking in females

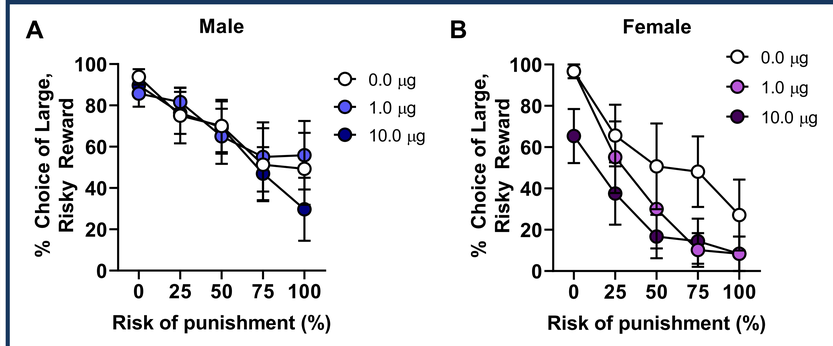


Figure 3: Microinfusions of quinpirole into the BLA decreased risk taking in females but not males. A. There was no significant effect of intra-BLA microinfusions of quinpirole in males [dose, F (2, 14) = 1.03, p = 0.38; dose X trial block, F (8, 56) = 1.64, p = 0.13]. **B.** Both the low and high doses of quinpirole caused a significant decrease in risk taking in females [low: dose, F (1, 4) = 8.63, p = 0.04, dose X trial block, F (4, 16) = 0.72, p = 0.59; high: F (1, 5) = 11.95, p = 0. 2, dose X trial block, F (4, 20) = 0.21, p = 0.93].

Intra-BLA D2R agonist alters win-stay and lose-shift behavior in females

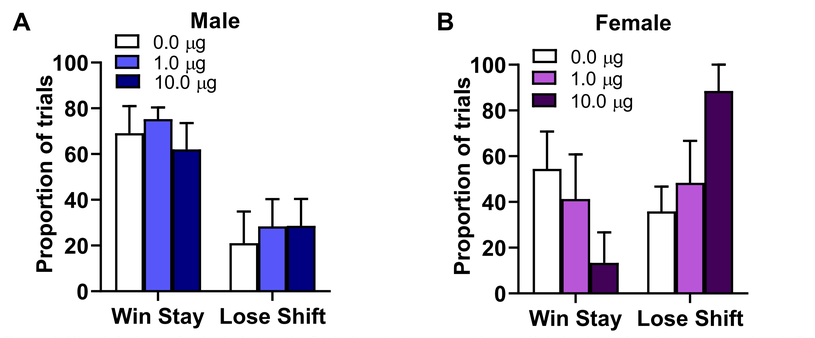


Figure 4: Microinfusions of quinpirole into the BLA altered win-stay and lose-shift behavior in females but not males. A. There was no effect of intra-BLA quinpirole on win-stay [dose, F (2, 12) = 0.03, p = 0.97] or lose-shift [dose, F (2, 12) = 0.06, p = 0.95] behavior in males. **B.** There was a main effect of intra-BLA quinpirole on win-stay [dose, F (2, 8) = 6.81, p = 0.02] and lose-shift [dose, F (2, 8) = 4.74, p = 0.04] behavior in females. Post-hoc analyses revealed that the highest dose of quinpirole decreased win-stay behavior [t (4) = 3.31, p = 0.03] and increased lose-shift behavior [t (4) = -5.10, p < 0.01].

Intra-BLA D2R antagonist did not affect risk taking

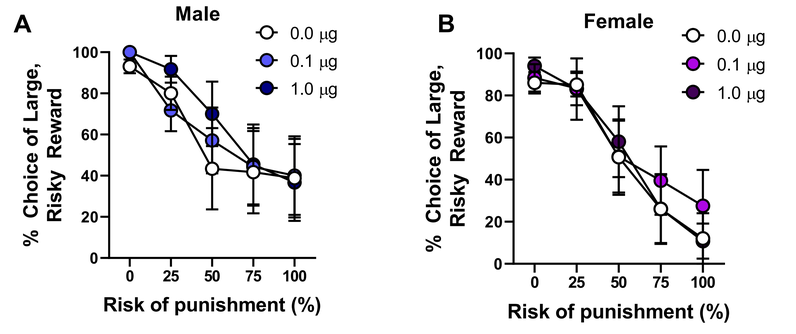


Figure 5: Microinfusions of eticlopride into the BLA had no effect on risk taking in males or females. A. There was no effect of intra-BLA microinfusions of eticlopride on risk taking in males [dose, F (2, 10) = 0.38, p = 0.69; dose X trial block, F (8, 40) = 0.76, p = 0.64]. **B.** There was no effect of intra-BLA microinfusions of eticlopride on risk taking in females [dose, F (2, 6) = 1.88, p = 0.23; dose X trial block, F (8, 24) = 0.88, p = 0.55].

Summary and Conclusions

- Systemic bromocriptine injections decreased risk taking
  - Bromocriptine decreased large lever presses in males only at the highest dose. In contrast, both the medium and high doses decreased large lever presses in females.
- Microinfusions of quinpirole into the BLA decreased risk taking only in females. This decrease in risk taking was accompanied by greater win-stay behavior and less lose-shift behavior.
- Microinfusions of eticlopride into the BLA had no effect on risk taking in either males or females.
- **Increased sensitivity of D2 dopamine receptors in the BLA contributes to greater risk aversion in females.**
- **This enhanced tone on D2 dopamine receptors arises from decreased reward sensitivity and enhanced sensitivity to negative feedback.**

Future Directions

- We will use a similar experimental design to investigate the contribution of D1 dopamine receptors in the BLA to risk taking in males and females.
- Future experiments will also use optogenetic manipulation of D2 receptor-expressing neurons in the BLA to determine whether these cells are recruited during selective epochs of the decision process.
- Sex differences in risk taking are mediated by gonadal hormones. Future work will therefore explore whether gonadal hormones, and estradiol in particular, regulate the sex differences in sensitivity to dopaminergic modulation of risk taking.

Acknowledgements

Supported by NIDA R00DA041493-3 (CAO) and Institute for Neuroscience NIH Institutional Training Grant T32DA018926 (LT).