Behavioral Effects of Dopamine Receptor Inactivation During the Adolescent Period: Age-Dependent Changes in Dorsal Striatal D2^{High} Receptors

Sanders A. McDougall, Joseph M. Valentine, Ashley E. Gonzalez, Danielle E. Humphrey, Crystal B. Widarma, Cynthia A. Crawford

Colors by Kelsey

Department of Psychology, California State University, San Bernardino

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Introduction

Irreversible receptor antagonists induce qualitatively different behavioral effects in young and adult rats. For example, systemic and intrastriatal injections of EEDQ attenuate the DA agonist-induced behaviors of adult rats; whereas, EEDQ potentiates NPA- and quinpirole-induced locomotor activity in preweanling rats. Why DA receptor inactivation augments the agonist-induced locomotor activity of preweanling rats remains uncertain. Our working hypothesis is that a greater percentage of DA receptors survive EEDQ-induced alkylation in young rats, relative to adults, and a disproportionate number of these surviving receptors exist in a high affinity state. Stimulation of these high affinity receptors is hypothesized to produce the potentiated locomotor response exhibited by young rats. Whether EEDQ attenuates or potentiates the locomotor activity of adolescent rats has not been assessed.

The purpose of the present study was twofold: First, to determine whether inactivating DA receptor in the dorsal striatum potentiates or attenuates the DA agonist-induced locomotor activity of adolescent rats. The second goal of this study was to determine whether those age groups exhibiting EEDQ-induced behavioral potentiation have a greater proportion of dorsal striatal D2^{High} receptors than adult rats.

Methods

In the behavioral experiment, stainless steel guide cannulae were implanted in the dorsal striatum on PD 38. EEDQ (50 or 100 µg) or DMSO were infused into the dorsal striatum 24 h later (i.e., on PD 39). After an additional 24 h, male and female adolescent rats were habituated to the testing apparatus for 40 min. Rats then received bilateral infusions of vehicle or NPA and locomotor activity was assessed for an additional 40 min.

For the D2 competition assays, rats were given an IP injection of vehicle or EEDQ (2.5 or 7.5 mg/kg) on PD 17 (preweanling), PD 39 (adolescent), or PD 84 (adult) and the dorsal striatum was removed 24 h later. Tissue was prepared and assays were conducted as described in Seeman (2008). Briefly, duplicate incubation tubes contained 0.15 ml of striatal homogenate, 1.2 nM [^{3}H]-domperidone, and various concentrations of DA. Nonspecific binding was determined in the presence of 10 µM (–)-sulpiride.

Results

The high dose of EEDQ (100 µg) significantly attenuated the basal and NPA-induced locomotor activity of male (Fig. 1) and female (Fig. 2) adolescent rats. Thus DA receptor inactivation affects adolescent rats in the same manner as adults, but unlike preweanling rats. Overall, NPA stimulated more locomotion in female adolescent rats than males. Among the control groups, adolescent rats had greater D2 specific binding than the other two age groups (Table 1). EEDQ reduced D2 receptor levels in the dorsal striatum of all age groups (Table 2), while increasing the proportion of D2^{High} receptors (Table 3). Regardless of pretreatment condition (i.e., DMSO or EEDQ), preweanling rats had a greater percentage of D2^{High} receptors than adolescent or adult rats.

Table 1. Mean D2 specific binding (fmol/mg wet weight tissue) in the dorsal striatum of DMSO-treated preweanling, adolescent, and adult rats (n = 8 per group).

Age group	Specific Binding
Preweanling	4.16 (±0.15) [a]
Adolescent	8.42 (±0.68) [ab]
Adult	6.18 (±0.38)

[a]Significantly different from adult rats.
[b]Significantly different from preweanling rats.

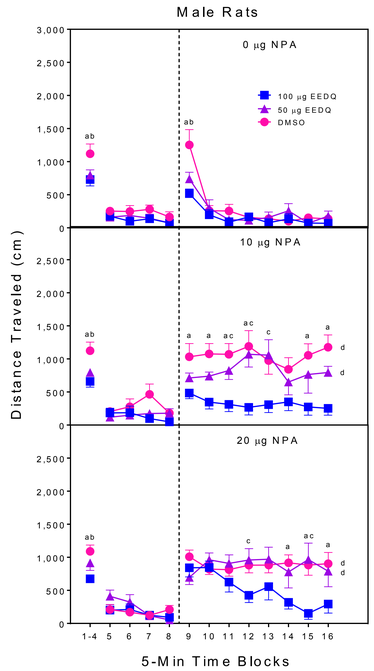

Fig. 1. [a]Significant difference between the DMSO and 100 µg EEDQ groups. [b]Difference between the DMSO and 50 µg EEDQ groups. [c]Difference between the 50 µg EEDQ and 100 µg EEDQ groups. [d]Significantly different from rats given 0 µg NPA.

Table 2. Mean D2 specific binding in the dorsal striatum of EEDQ-treated preweanling, adolescent, and adult rats expressed as the percent of DMSO controls.

Age group	EEDQ (mg/kg)		
	0	2.5	7.5
Preweanling	100%	56.4%	46.8%
Adolescent	100%	47.2% [a]	33.3% [a]
Adult	100%	52.6%	40.1%

[a]Significantly different from preweanling rats.

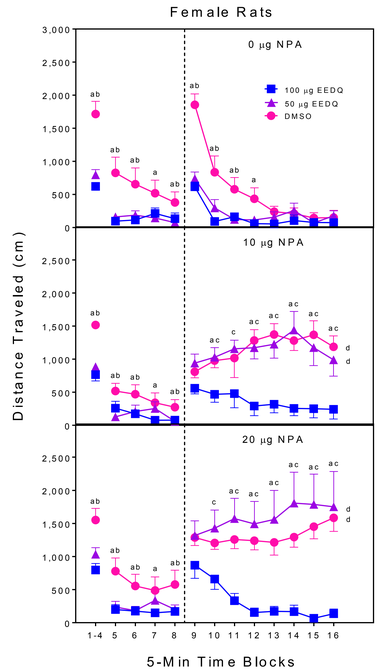

Fig. 2. [a]Significant difference between the DMSO and 100 µg EEDQ groups. [b]Difference between the DMSO and 50 µg EEDQ groups. [c]Difference between the 50 µg EEDQ and 100 µg EEDQ groups. [d]Significantly different from rats given 0 µg NPA.

Table 3. Percent D2^{High} receptors in the dorsal striatum of EEDQ-treated preweanling, adolescent, and adult rats.

Age group	EEDQ (mg/kg)		
	0	2.5	7.5
Preweanling	29.0 [a]	51.5 [a]	51.3 [a]
Adolescent	21.6	42.8	45.8
Adult	20.8	42.1	44.8

[a]Significantly different from adolescent and adult rats.

Discussion

- EEDQ's ability to reduce NPA-induced locomotion was apparent in both male and female adolescent rats, and is essentially the same pattern of results reported for adult rats.
- Thus, adolescent and adult rats respond in a similar manner after DA receptor inactivation; it is only during the earlier preweanling period that EEDQ causes a paradoxical increase in basal and DA agonist-induced locomotor activity.
- We have proposed that the EEDQ-induced behavioral potentiation observed in preweanling rats is due to (1) a greater percentage of DA receptors surviving EEDQ-induced alkylation and (2) a disproportionate number of these surviving receptors existing in a high affinity state.
- The present results are consistent with this explanation since EEDQ-induced D2 receptor inactivation was less extensive in preweanling rats than adolescents, while the younger age group had a greater percentage of D2^{High} receptors than adolescent or adult rats.
- Consistent with previous studies, the D2 specific binding of nonEEDQ-treated adolescent rats was significantly elevated relative to both younger and older rats.

References

Seeman P (2008) Dopamine D2$^{(High)}$ receptors moderately elevated by bifeprunox and aripiprazole. Synapse 62:902–908.

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