Rat strain sensitivity to startle-enhancing effects of D1 stimulation vs. gating-disruptive effects of D2 stimulation

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Abstract

BACKGROUND: Outbred rat strains differ in the behavioral sensitivity to dopamine (DA) agonists. For example, we reported significantly greater sensitivity to the prepulse inhibition (PPI)-disruptive effects of D2-family agonists in Sprague-Dawley (SD) vs. Long Evans (LE) rats; this sensitivity is heritable, and appears to reflect differential activation of DA signaling in the nucleus accumbens (NAC). Our studies utilizing a mixed D2/D1 agonist, apomorphine (APO), have often detected startle-enhancing effects of APO in LE rats vs. no effects, or even startle-suppressing effects, in SD rats. Here, we tested whether these strains differ in sensitivity to the startle-enhancing effects of D1 stimulation, and whether this phenotype is separable from changes in PPI.

METHODS: Startle magnitude and PPI were assessed in male SD and LE rats after treatment with the D1-preferential agonist, SKF 81297 (0.3, 1.0, 3.0 mg/kg sc), using 85 dB(A) prepulses and 95-120 db(A) startle pulses over a 70 dB(A) background. Startle-enhancing effects of SKF 81297 were also tested in LE rats after pretreatment with the D1-preferential antagonist, SCH23390 (0.05 mg/kg sc).

RESULTS: SKF 81297 significantly potentiated startle in LE but not SD rats, and had no significant effect on PPI in either strain. ANOVA of startle magnitude revealed significant interactions of dose x strain and dose x strain x pulse intensity (p's < 0.0001); post-hoc comparisons detected startle-potentiating effects of SKF 81297 only in LE rats, at 1.0 and 3.0 mg/kg doses. These startle-potentiating effects of SKF 81297 (1.0 mg/kg) were prevented by pretreatment with SCH23390.

DISCUSSION: Strain differences in the DAergic regulation of startle phenotypes exhibit a complementary pattern, with SD > LE sensitivity to the PPI-disruptive effects of D2 stimulation, and LE > SD sensitivity to the startle-enhancing effects of D1 stimulation. In the case of PPI, this differential D2 sensitivity appears to reflect differences in NAC gene expression and D2-signaling, but the neural basis for differential D1 startle sensitivity is not known. We reported LE > SD sensitivity to the startle-enhancing effects of mild restraint stress; based on this and convergent pharmacological data, we are now examining the role of the amygdala in the differential expression of D1-potentiated startle in SD vs. LE rats.

Introduction

The acoustic startle response (ASR) is a reflex contraction of skeletal and facial muscles in response to an intense noise burst. The ASR is detected across mammalian species and has many heritable features in both rodents and humans. We reported that commonly-studied outbred rat strains differ in their sensitivity to dopamine (DA) agonist-induced changes in the ASR and its modification by prestimuli, termed "prepulse inhibition " (PPI). Specifically, albino Sprague Dawley (SD) rats are more sensitive to the PPI-disruptive effects of DA agonists, compared to hooded Long Evans (LE) rats. This phenotype is heritable, and reflects differential D2 signaling in the nucleus accumbens (NAC) and its impact on downstream GABA release; it is being explored as a model for heritable differences in PPI in human brain disorders, including schizophrenia. In the context of these studies, we also reported greater sensitivity to the startle magnitude-potentiating effects of the mixed D1/D2 agonist, apomorphine (APO), in male LE vs. SD rats, with an intermediate phenotype in F1 (SD x LE) males (Figure 1). Because SD rats are more sensitive to the D2-mediated PPI-disruptive effects of APO, we hypothesized that greater startle-potentiating effects of APO in LE rats reflected a relatively enhanced D1 sensitivity in LE vs. SD rats. In these new studies, we tested this hypothesis.

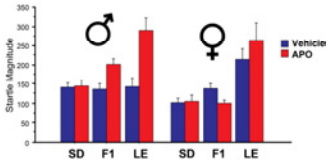

Figure 1. Example of startle-potentiating effects of the mixed D1/D2 agonist, apomorphine, in male LE but not SD rats. The phenotype is intermediate in male F1 (SD x LE) rats, and is sex-specific to males.

Methods

Male SD and LE rats (225-249 g) were administered SKF 81297 (veh, 0.3,1.0, 3.0 mg/kg sc) 10 min prior to startle and PPI testing in a within-subject design, with 4 d between testing. After receiving SKF or vehicle, the rats were exposed to a 70 dB(A) background noise, then received a brief habituation block and an active block with 8 repetitions of pulse trials of 95, 100, 105, 110, 115 and 120 db(A) 40 ms pulses, and PPI trials of 105 and 120 dB(A) pulses preceded 100 ms by a 15 dB-over-background 20 ms prepulse. Separate LE rats were tested in this paradigm after being pretreated with SCH 23390 (veh or 0.05 mg/kg sc) and 10 min later treated with SKF 81297 (veh or 1.0 mg/kg) in a 2d-within-subject design. In other SD and LE rats, startle testing followed treatment with the D2-selective agonist, sumanirole. Finally, cFOS expression was assessed in the NAC core and shell and basolateral amygdala (BLA) in SD and LE rats, after treatment with SKF 81297 (veh or 1.0 mg/kg) and exposure to a "mock" startle session.

Results

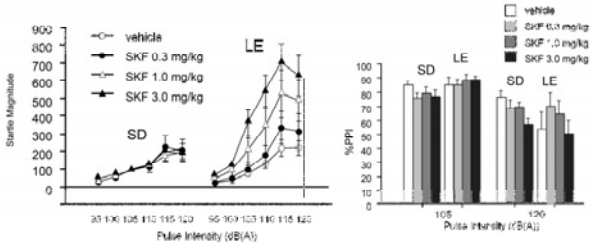

Figure 2. Effects of the D1-preferential agonist, SKF 81297, on startle magnitude (left) and PPI (right) in SD and LE rats. This D1 agonist significantly enhanced startle magnitude in LE but not SD rats, an effect that reached significance for 1.0 and 3.0 mg/kg doses in LE rats. In contrast, SKF 81927 did not significantly reduce PPI in either rat strain, though a trend towards reduced PPI was detected in SD rats with 120 dB(A) startle pulses.

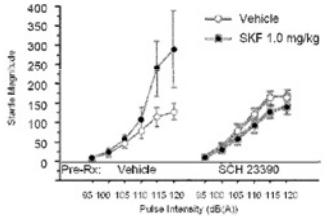

Figure 3. Pretreatment with the D1 antagonist, SCH 23390, prevents the startle-potentiating effects of SKF 81297 in LE rats. In rats pretreated with vehicle, SKF 81297 significantly potentiated startle (left), but this effect was blocked by SCH 23390 (right).

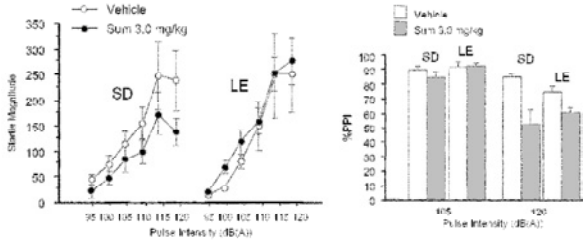

Figure 4. Effects of the D2-selective agonist, sumanirole (Sum), on startle magnitude (left) and PPI (right) in SD and LE rats. D2 stimulation reduced startle magnitude in SD but not LE rats (left). Sum reduced PPI when 120 dB pulses were used, and this effect was more robust in SD vs. LE rats (right).

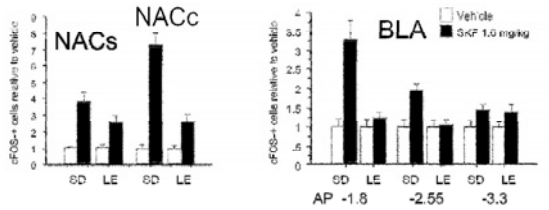

Figure 5. Effects of the D1-preferential agonist, SKF 81297, on cFOS activation (# positive cells relative to vehicle) in the NAC shell and core and BLA, in SD and LE rats. Interestingly, the effects of D1 stimulation on FOS expression were significantly greater in SD vs. LE rats in both the NAC and BLA, the latter effects being most evident in rostral portions of the BLA. In previous reports, DA agonists that disrupt PPI in SD rats (e.g. the mixed D1/D2 agonist, APO, and the D3/D2 agonist, pramipexole) were noted to *suppress* FOS expression in the NAC.

Discussion

We tested the hypothesis that LE rats are more sensitive than SD rats to the startle-enhancing effects of D1 receptor stimulation. Findings support this hypothesis. Specifically:

1. LE rats, but not SD rats, exhibit a robust, dose-dependent enhancement of startle magnitude in response to the D1-preferential agonist, SKF 81297;
2. The startle-potentiating effects of SKF 81297 in LE rats are blocked by pretreatment with the D1-preferential antagonist, SCH 23390;
3. By contrast, the D2-selective agonist, sumanirole, does not enhance startle in LE rats, and suppresses startle magnitude in SD rats. These changes occur at a dose that significantly reduces PPI, and are generally consistent with previous findings suggesting SD > LE sensitivity to D2 stimulation.

In contrast to behavioral effects of D1 stimulation, SKF 81297 significantly enhanced FOS expression in the NAC and BLA, and these effects were greater in SD vs. LE rats. These findings do not provide a parsimonious mechanism for the observed behavioral phenotypes, based on differential sensitivity to D1 activation in the NAC or BLA. While the mechanism is not yet clear, these findings do suggest a heritable "trade-off" in behavioral sensitivity to forebrain D1 vs. D2 stimulation in LE vs. SD rats, among behaviors relevant to heritable features of human psychopathology.

References

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Conflicts of Interest: None