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Differential effects of a selective dopamine D1-like receptor agonist on motor activity and *c-fos* expression in the frontal-striatal circuitry of SHR and Wistar-Kyoto rats

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Abstract

Background: Molecular genetic studies suggest the dopamine D1 receptor (D1R) may be implicated in attention-deficit/hyperactivity disorder (ADHD). As little is known about the potential motor role of D1R in ADHD, animal models may provide important insights into this issue.

Methods: We investigated the effects of a full and selective D1R agonist, SKF-81297 (0.3, 3 and 10 mg/kg), on motor behaviour and expression of the plasticity-associated gene, *c-fos*, in habituated young adult male Spontaneously Hypertensive Rats (SHR), the most commonly used animal model of ADHD, and Wistar-Kyoto (WKY; the strain from which SHR were derived).

Results: SHR rats were more behaviourally active than WKY rats after injection with vehicle. The 0.3 mg/kg dose of SKF-81297 increased motor behaviour (locomotion, sifting, rearing, and sniffing) in both SHR and WKY rats. Total grooming was also stimulated, but only in WKY rats. The same dose increased *c-fos* mRNA expression in the piriform cortex of both strains. The 3 mg/kg dose increased sifting and sniffing in both strains. Locomotion was also stimulated towards the end of the testing period. The intermediate dose decreased total rearing in both strains, and produced a significant increase in c-fos mRNA in the striatum, nucleus accumbens, olfactory tuberculum, and in the cingulate, agranular insular and piriform cortices. The 10 mg/kg dose of SKF-81297 produced a biphasic effect on locomotion, which was characterized by an initial decrease followed by later stimulation. The latter stimulatory effect was more pronounced in SHR than in WKY rats when compared to their respective vehicle-injected groups. The 10 mg/kg dose also stimulated sifting and sniffing in both strains. Both the 3 and 10 mg/kg doses had no effect on total grooming. The 10 mg/kg dose induced significantly higher levels of *c-fos* mRNA expression in the nucleus accumbens and adjacent cortical regions (but not striatum) of SHR when compared to WKY rats.

Conclusion: The present results suggest a potential alteration in D1R neurotransmission within the frontal-striatal circuitry of SHR involved in motor control. These findings extend our understanding of the molecular alterations in SHR, a heuristically useful model of ADHD.