SKF83959, a unique anti-Parkinson agent in animal models, stimulates dopamine D1 receptors that are coupled to phospholipase C, in denervated striatum and intact nucleus accumbens of freely moving rats

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SKF83959 has anti-Parkinson effects in the best animal model of Parkinson's disease, namely the MPTP-lesioned rhesus monkey, without producing serious side-effects. In vitro studies have shown that this drug acts both as an antagonist of the D1 receptors coupled to adenylyl cyclase (D1ac), and as an agonist of the D1 receptors coupled to phospholipase C (D1plc). The target sites of the anti-Parkinson effects of this drug in animals are unknown. SKF83959 is already known to act as an in vivo antagonist of D1ac receptors in both the prefrontal cortex and the nucleus accumbens. To understand its anti-Parkinson effects, we performed four additional rotation studies. (A) We determined that its unilateral administration into the striatum or nucleus accumbens of naive rats was ineffective. (B) We determined that its unilateral intra-accumbens administration elicited contralateral turning, when combined with the dopamine D2 agonist Quinpirole; this effect was inhibited by SCH 23390, an aselective antagonist of dopamine D1 receptors. Quinpirole itself was ineffective in inducing turning behaviour. It is concluded that the turning was elicited by stimulation of D1plc receptors. (C) We determined that the mentioned accumbens treatment reduced the extracellular amount of dopamine in the ipsilateral ventrolateral striatum, turning down the hypothesis that SKF83959 produced its turning via the accumbens-nigro-striatal circuitry. (D) We determined that unilateral striatal administration of SKF83959 produced contralateral turning in the unilaterally 6-hydroxydopamine lesioned rat, an effect that was inhibited by SCH 23399, showing that also this effect was mediated by stimulation of the D1plc receptor. We hypothesize that the unique anti-Parkinson profile of SKF83959 is due to the combined ability to inhibit the D1ac receptors and to stimulate the D1plc receptors.

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