Repeated ropinirole treatment resulting in recovery of sensorimotor gating induces ΔFosB in mouse nucleus accumbens neurons that co-express D1 and D3 dopamine receptors, but not D2 receptors.

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BACKGROUND

- Prepulse inhibition (PPI), a behavioral task indicative of sensorimotor gating deficits in schizophrenia, is reduced by acute treatment with a D3-like receptor agonist (Martinez, Ellison, Geyer, & Swerdlow, 1999), or by its local administration in the nucleus accumbens (NAc) (Wan & Swerdlow, 1993).
- By contrast, repeated treatment with quinpirole or ropinirole causes PPI recovery lasting up to four weeks after termination of treatment in rats (Berger, Green, Siegel, Nestler, & Hammel, 2011; Culm, Lugo-Escobar, Hope, & Hammer, 2004).
- Repeated quinpirole treatment induces activation of the cyclic AMP (cAMP) pathway as evidenced by an increase of cAMP-dependent protein kinase (PKA) activity and CREB phosphorylation in the NAc (Culm & Hammer, 2004).
- We have demonstrated that repeated quinpirole treatment induces prolonged expression of ΔFosB, a truncated splice variant of FosB protein, in the NAc. ΔFosB is induced by chronic activation of cAMP signaling, has extended stability, and is implicated in long-term behavioral adaptation (Nestler, Barrot, & Self, 2001).
- In the NAc, ΔFosB induction has different behavioral effects depending on whether it is present in D1-like or D2-like dopamine receptor-expressing neurons (Grueter, Robison, Neve, Nestler, & Malenka, 2013).

METHODS

Animals and Drug Treatment

Adult male IAC transgenic mice that express either D1R-DsRed or eGFP in striatal neurons containing dopamine 1 receptor cell subtype (D1R-DsRed or eGFP) (Gong et al., 2003) were treated with saline or ropinirole (0.1 mg/kg, ip) for 28 days.

Histology

Seven days after termination of drug treatment, mice were anesthetized and perfused with 4% buffered paraformaldehyde. Striatal brain sections (40 μm) were collected and stored in cryopreservative at 4°C prior to processing. Sections were washed three times in 0.05 M potassium phosphate buffered saline (KPBS, pH 7.4), and incubated in 5% normal goat serum (0.05 M KPBS, 0.4% Triton X (NGS/KPBS/TX)) for 60 min at room temperature.

To determine ΔFosB labeling, primary antibody raised against the N-terminal region of FosB (SC-48; Santa Cruz Biotechnology, Santa Cruz, CA) was used at a dilution of 1: 12,000 (in NGS/KPBS/TX). This antibody recognizes 32-37 kDa proteins corresponding to the molecular weight of ΔFosB-like proteins, as well as full-length FosB (Perrett et al., 2004). Primary antibody was raised against the dopamine 3 receptor subtype (D3; SC-9114; Santa Cruz Biotechnology, Santa Cruz, CA) was used at a dilution of 1: 20 in NGS/KPBS/TX to determine D3R labeling.

Staining

Brain sections on slides were analyzed at 20X magnification using a Zeiss microscope and Image J Software. A modified stereological approach was employed to randomly assess neuronal labeling density. The total number of labeled neurons was analyzed using two-way ANOVA.

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REFERENCES

SUMMARY AND CONCLUSIONS

- Repeated ropinirole treatment induced ΔFosB selectively in NAc neurons of both D1R-DsRed and D2R-eGFP mice, confirming our prior results.
- Repeated quinpirole treatment significantly increased the percentage of ΔFosB in NAc neurons which co-expressed D1 and D2 receptors.
- Repeated activation by ropinrole of heterodimeric D1/D2 receptors in NAc neurons could drive D1 receptor coupling, which could underlie increased phosphoCREB and ΔFosB expression required for PPI recovery.