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Effects of dopaminergic agonists on prepulse inhibition of the startle reflex in man

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Background

The startle reflex is inhibited when the startling eliciting stimulus is preceded by a weak prepulse in the same or different modality. This phenomenon is termed Prepulse Inhibition (PPI) of the startle reflex and is used as a cross-species operational measure of sensorimotor gating functions, which normally prevent the organism from overload of information. PPI is equally disrupted in patients with schizophrenia spectrum disorders, and in experimental animals with central dopamine activation caused by drugs, which facilitate dopaminergic neurotransmission and this disruption is reverced by neuroleptics. The few human PPI studies with dopaminergic drugs, have produced inconsistent rersults so far: Bromocriptine was found to disrupt PPI or to have no effect, while pergolide and amantadine had no effect. In this study we report in three separate experiments, the effects of pergolide, amantadine and ropinirole, all of which are drugs with known dopaminergic neurotransmission facilitatory properties.

Material and Methods

In Experiment 1, 12 healthy male volunteers (21–29 years) participated in 3 sessions, in which they received pergolide 0.05 mg, pergolide 0.1 mg and placebo. In Experiment 2, 12 healthy males (20–31 years) received ropinirole 0.25 mg, ropinirole 0.5 mg and placebo and in Experiment 3, 16 healthy males (20–28 years) were administered amantadine 100 mg, amantadine 200 mg and placebo. In all 3 experiments subjects were allocated to sessions and treatments according to a balanced, cross-over, double blind design. In all 3 experiments electromyographic responses of the orbicularis oculi muscle were recorded for 17 min, at 2, 1.5 and 3 hours after treatment for each experiment respectively. The startle testing session consisted of a block of 5 pulse-alone stimuli at the beginning and at the end of the 17 min recording, for the assessment of baseline startle and startle habituation. In between these blocks, subjects received 42 trials of pulse-alone and prepulse-pulse stimuli. Pulses comprised 115 dB, 40 msec bursts of white noise and prepulses were 75 and 85 dB, 20 msec bursts of white noise with prepulse-pulse intervals of 30 and 60 msec. Pulse-alone and prepulse-pulse trials were presented in a pseudorandom order at an inter-trial interval averaging 15 sec.

Results

For each separate experiment, baseline startle was analysed by 2-way repeated measures ANOVA (treatment × block). %PPI data were analysed by 3-way repeated measures ANOVA (treatment × prepulse × prepulse-pulse interval). Pergolide but not amantadine or ropinirole reduced baseline startle in a dose-dependent manner but did not affect startle habituation. The analysis of the %PPI data showed significant main effects of prepulse ($p < 0.005$) and interval ($p < 0.05$) in the case of pergolide and amantadine but no main effect of treatments or interactions. There was a trend for amantadine to increase PPI. Ropinirole 0.5 mg decreased %PPI at the 60 msec inter-stimulus interval for both 75 and 85 dB prepulses, as confirmed by a statistically significant treatment × interval interaction ($p < 0.05$).

Discussion

The different mechanisms of action of the three drugs may be responsible for the success of ropinirole (a selective D_2 agonist) and the failure of pergolide (a D_1 and D_2 agonist) andamantadine (presumably an indirect dopamine agonist and an uncompetitve NMDA antagonist) to reduce

PPI. These findings suggest, in agreement with pre-clinical studies, that PPI in humans is modulated through the D_2 subtype of dopamine receptors.