INTRODUCTION

While testosterone promotes aggression, serotonin exerts the opposite effect. If testosterone influences brain serotonergic activity, one possible mechanism of action for the hormonal pro-aggressive effect would be that it might counteract an anti-aggressive effect of serotonin.

The aim of this study was to explore this possibility, following the rationale that: if testosterone does exert its pro-aggressive effect by dampening serotonergic transmission, then i) the anti-aggressive effect of anti-androgenic interventions would be counteracted by serotonin depletion, and ii) administration of testosterone would fail to cause any further increase in aggression in serotonin-depleted animals.

To examine this, we assessed if serotonin depletion, induced by administration of the tryptophan hydroxylase inhibitor p-chlorophenylalanine (p-CPA), restores aggression in gonadectomized mice and in mice displaying brain-specific knockout of androgen receptors (ARneoDel), respectively, and also to what extent the pro-aggressive effect of exogenously administered testosterone in the former group is dependent on the presence of serotonin.

RESULTS

Experiment I. In testosterone treated mice, p-CPA led to a significant increase in both frequency and duration of aggressive acts while it was completely void of effects in mice not treated with hormones (Fig. 1A).

Experiment II. ARneoDel mice displayed low levels of aggressive behaviour in both tests and was not affected by p-CPA-treatment. In the control group, although duration of aggression was robustly increased by p-CPA treatment, this measure failed to reach significance (Fig 2A). However, compared to saline treated controls, there was a significantly greater number of mice attacking within 200 seconds (Fig. 2B).

METHODS

Experiment I. Male C57Bl/Kin mice (Charles River, Denmark), were gonadectomized and implanted with slow-release pellets containing testosterone (15 mg/60days) or placebo (Inovative Research of America, USA) after 2 weeks of recovery. The dose was chosen to be in the high range of the physiological interval and have been shown to reliably increase aggression in castrated male mice (1). After 2 additional weeks, mice were housed individually for nine days before resident intruder test and p-CPA treatment.

Experiment II. ARneoDel mice were generated as described previously (2). Briefly, ARneo female mice were bred with male Nestin-Cre mice. Immature ARneo mice and littermate controls were housed individually for 23 days and tested in the resident intruder test.

COMMENT

The observation that the marked reduction in aggression exerted by gonadectomy or brain-specific androgen receptor knockout was not counteracted by serotonin depletion permits the conclusion that the pro-aggressive effect of testosterone is not primarily caused by an inhibition of serotonergic transmission.

Similarly, testosterone was found to exert a marked aggression-provoking effect also in the absence of this transmitter; this behavioural effect of the hormone was in fact more pronounced in p-CPA-treated animals than in controls, suggesting that serotonin exerts parallel-coupled inhibitory influence on testosterone-induced aggression, causing serotonin depletion to enhance aggression in the presence but not in the absence of androgen receptor activation.