

Endocrine and behavioural effects of acute and repeated oral administration of the antigluocorticoid RU486 in male C57BL/6J mice

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Corticosteroid hormones secreted by the adrenals protect the brain against adverse events and are essential for cognitive performance. The effects depend on context and the balanced activation of mineralo(MR) and glucocorticoid receptors (GR; deKloet, TINS1999). Recently, oral administration of the antiGR RU486, resetted high to normal cortisol and rapidly attenuated negative behavioural symptoms in patients with psychotic major depression (Belanoff, BiolPsych, 2002). The aim of the present study was to shift the MR/GR balance using a non-invasive, stress-free oral application of RU486 (acute and repeated GR blockade) in mice to assess the duration of endocrine changes and behaviour during the first exposure to a spatial learning task. Mice readily consumed 3 pieces of oat (~120 mg), containing vehicle or 200 mg/kg RU486. Corticosterone was measured in blood at 1, 2, 3, 4, 8 hrs after consumption. As expected, corticosterone remained low in vehicle-treated mice (~50 ng/ml), with the circadian increase at 1700 hrs. RU486 boosted corticosterone up to 300 ng/ml persistently over 4 hrs, and also increased the amplitude at the circadian peak at 1700 hrs. Repeated RU486, once daily at 1700 hr for 4 days, didn't affect basal corticosterone and ACTH 16 hrs later (day 5 at 0900). Observing the RU486 mice for 5 min on the circular hole board revealed a distinct exploration strategy: the center was left earlier, more holes were visited using a serial strategy, while general activity was similar. In summary, oral RU486 via oats increased corticosterone for at least 8 hrs. The directed exploratory behaviour indicates changes in cognitive processes of perception and response selection, indicating a shift in the MR/GR balance towards a more prominent role of MR. Whether learning and memory are affected as well, will be addressed in future experiments.

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