ABSTRACT

Gender and Gonadal Hormonal Variations Influence Learning Behaviour: Interactions of the Mesolimbic Dopaminergic System

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Given the existence of a neuroendocrinological link in certain neurological disorders, this study was designed to investigate whether gender or the female sex hormones modulate mesolimbic dopaminergic activity during the processing of avoidance learning and memory. Rats were divided into males, estrous and diestrous females and further sub-divided into lesioned and sham-lesioned rats, treated with amphetamine (1 mg/kg/ml, i.p.), cocaine (1 mg/kg/ml, i.p.) or saline. Mesolimbic lesioning was achieved with the administration of 6-hydroxydopamine at the level of the nucleus accumbens septi (NAS). Rats were confined to a discriminable arm of a Y-maze and exposed to 3 min of electric foot-shock or not shocked (controls). Rats were returned to the Y-maze a day later (Trial 1) and 2 weeks subsequently (Trial 2) to assess their exploratory and avoidance behaviours. Estradiol benzoate (10 μg/kg/ml, s.c.), progesterone (5 mg/kg/ml, s.c.), estradiol benzoate followed by progesterone, or corn oil were administered to ovariectomized rats and the exploratory and avoidance behaviours were determined as before and at 30 min (Trial 0) post-training. Also, *in vivo* microdialysis was used to quantify dopamine (DA), and its breakdown products dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), in the NAS of ovariectomized rats, pretreated with the female sex hormones. Simultaneously, locomotor activity was assessed before and after foot-shock. Gender did not

significantly increase exploratory behaviour or avoidance behaviour in response to foot-shock. However, estrous rats demonstrated significant impairment in avoidance learning. Estrogen administration improved avoidance learning. Amphetamine and cocaine accentuated the differential in the hormonal effects of avoidance behaviour, while NAS lesioning diminished the hormonal effects and potentiated learned helplessness. NAS DA levels were decreased significantly to similar levels in estrogen and estrogen/progesterone pretreated animals; but locomotor activity was high in the former group and low in the latter. Progesterone treatment lowered both NAS DA and locomotor activity levels. These differences may be due to "discriminative" modulation of the mesolimbic dopaminergic system by the sex hormones, that is, in different ways. These findings support the influence of the estrous cycle on learning and memory and a modulatory role of gonadal hormones and the mesolimbic dopaminergic system in avoidance learning and memory.

Keywords: Liris Carlotta Benjamin; sex hormones; nucleus accumbens septi (NAS); learning and memory