Thesis Title Early Environmental Influence on the Responsiveness to Antianxiety Drugs in the Adult Rats

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Abstract

Environments during the early stages of life have profound consequences for behaviour in the later life of most mammals and altered the responsitivity to psychotropic drugs. The aims of this thesis were to determine whether social isolation in the early stage of life causes long term alterations in subsequent behavioural pattern of adult rats and to investigate the effects of social isolation on the responsitivity to midazolam, the short acting benzodiazepine; clonidine, the selective α_2-adrenoceptor agonist, buspirone, the 5-HT_{1A} receptor partial agonist, and 8-OH-DPAT, the selective 5-HT_{1A} receptor agonist.

Male Wistar rats were reared from 21 days (weaning) either alone (isolation reared rats) or in groups of five (socially reared rats) for five weeks. Each rat was placed onto the elevated plus maze (the animal model of anxiety) or into the open field arena (the animal model of locomotor activity) either without drug pretreatment or following systemic administration of saline or drugs, 30 min before a 5 min test.

The present experiments show that isolation reared rats produced anxiogenic profile compared to socially reared rats on the elevated plus maze, and had no marked effect on locomotor activity testing in the open field arena, under high light and unfamiliar conditions.

Midazolam (0.5, 1 and 2 mg/kg i.p.) dose-dependently produced anxiolytic effect on the rat elevated plus maze as indicated by increasing the

percentage of open : total arm entries and time spent in both socially and isolation reared rats. These anxiolytic profiles were greater in isolation than socially reared rats. At low dose, midazolam (0.5 mg/kg) produced hyperlocomotor activity only in socially reared rats as indicated by the increase in the total arm entries and the total zone transitions. However, at the highest dose, midazolam (2 mg/kg) produced hypolocomotor activity in both groups.

Clonidine (0.01, 0.03 and 0.05 mg/kg i.p.) produced anxiolytic effect in both isolation and socially reared rats. These effects of clonidine were more pronounced in isolation than socially reared rats. Clonidine decreased locomotor activity as indicated by decreasing the total arm entries and the total zone transitions in both isolation and socially reared rats.

Buspirone (0.1, 0.5 and 1 mg/kg i.p.) had no marked effect on the rat elevated plus maze and the open field behaviours in both isolation and socially reared rats.

8-OH-DPAT (0.05, 0.1 and 0.5 mg/kg s.c.) produced a dose related anxiogenic effect in both socially and isolation reared rats as indicated by decreasing the percentage of open : total arm entries and time spent. These effects were greater in isolation than socially reared rats. Low doses of 8-OH-DPAT (0.05 and 0.1 mg/kg) had no marked effect on locomotor activity. However, the highest dose of 8-OH-DPAT (0.5 mg/kg) produced the hypolocomotion-like effect on the plus maze (decreased the total arm entries). This effect was more pronounced in isolation than socially reared rats. However, 8-OH-DPAT produced hyperlocomotion profile in the open field arena (increased the total zone transitions) in both groups. Thus, the effect of 8-OH-DPAT on the locomotor activity depended upon the test apparatus.

All results demonstrate that isolation reared rats exhibited anxiogenic profiles and were more sensitive to the anxiolytic effect of midazolam and clonidine, and the anxiogenic effect of 8-OH-DPAT. A possible explanation for these effects is an alteration of the central neurotransmitter mechanisms e.g. presynaptic α_2-adrenoceptor and postsynaptic 5-HT_{1A} receptor supersensitivity etc. Further experiments will be needed to determine whether there are alterations in brain benzodiazepine receptors or GABA receptors functions in isolation reared rats.