Thesis Title Functional Interactions between Noradrenaline and Serotonin and Their Involvement in Anxiety

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Date of Graduation : 10 August B.E. 2535 (1992)

ABSTRACT

The present studies have validated the elevated plus-maze as an animal model test capable of detecting not only the anxiolytic effects of the benzodiazepine diazepam but also non-benzodiazepine compounds such as a selective alpha 2-adrenoceptor agonist, clonidine. It can detect the anxiogenic effect of a selective alpha 2-adrenoceptor antagonist, idazoxan and the 5-HT_{1C} receptor agonist, mCPP. However, it is insensitive to detect an anxiolytic effect of the 5-HT_{1A} partial agonist, buspirone.

The present results demonstrated that diazepam dose-dependently produced anxiolytic profiles on the rat elevated plus-maze. This was indicated by an elevation of the percentage of open arm entries, the percentage of time spent on the open arms, and time spent on the end of the

open arms, without effect on the total arm entries and the number of rears/min. In contrast, idazoxan and mCPP had the opposite effect, both drugs dose-dependently produced an anxiogenic effect.

Pretreatment with diazepam 30 min before administration of either idazoxan or mCPP not only prevented the anxiogenic effect of idazoxan and mCPP but these two drugs also blocked the anxiolytic effect of diazepam. mCPP dose-dependently antagonized the anxiolytic effect of diazepam. The results suggest that the anxiolytic effect of benzodiazepines may in part be due to the modulatory effect of the benzodiazepine on the noradrenergic and serotonergic systems.

Clonidine, in a narrow low dose range, had an anxiolytic effect whereas sedation and hypolocomotor activities were observed in higher doses. These effects were antagonized by idazoxan. Simultaneously the anxiogenic effect of idazoxan was also prevented by pretreatment with clonidine. These results suggest that pharmacological antagonism occurs on the same type of receptor : clonidine exerts it effects probably by stimulation the presynaptic alpha 2-adrenergic autoreceptors whereas idazoxan exerts anxiogenic effect possibly by inhibition at those same receptors.

Pretreatment with clonidine not only prevented the anxiogenic effect of mCPP but mCPP also antagonized the anxiolytic action of clonidine. Moreover, the combination

of idazoxan and mCPP significantly produced an anxiogenic effect. These results suggest the functional linkage between the noradrenergic and serotonergic systems in the involvement of anxiety.

Using HPLC-EC to measure the brain levels of 5-HT and 5-HIAA ex vivo , it was found that idazoxan dose-dependently increased 5-HT release and turnover in the rat hippocampus and brain stem. The results were correlated with the dose-dependent anxiogenic effect of idazoxan in the elevated plus-maze. These findings suggest that idazoxan may antagonize the presynaptic inhibitory alpha 2-adrenergic heteroceptors located on 5-HT neurones resulting in increased 5-HT activity and hence anxiety.

All results obtained reinforce the idea of the functional interactions between the noradrenergic and serotonergic systems in the control of anxiety.