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SELECTIVE INCREASE IN DOPAMINE METABOLISM IN THE PREFRONTAL CORTEX BY THE ANXIOGENIC BETA-CARBOLINE FG 7142

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Several studies have demonstrated that the mesocortical dopamine (DA) neurons projecting to the prefrontal cortex are activated in response to stress. Electric footshock increases DA metabolism in these neurons, and such changes can be reversed by benzodiazepines [1,2,3]. Recent studies have also shown that these neurons are selectively activated by conditioned stress as elicited by exposure to a neutral stimulus previously paired with footshock, thus implicating the involvement of the prefrontal DA system in fear or anxiety [4,5].

It is now generally accepted that the pharmacological effects of the anxiolytic benzodiazepines are mediated through specific receptors in the central nervous system. Beta-carboline carboxylate esters are specific benzodiazepine receptor ligands which antagonize the various central effects of benzodiazepines [6]. Moreover, some beta-carbolines have been found to be anxiogenic in animals and in humans [7,8,9]. In light of our recent finding of a benzodiazepine receptor modulation of the prefrontal DA system [10], we have examined whether an anxiogenic beta-carboline, FG 7142 (methyl-beta-carboline-3-carboxamide), could activate these DA neurons in a fashion similar to that produced by stress.

MATERIALS AND METHODS

Male Sprague-Dawley rats weighing 350-375 g were obtained from Camm (Wayne, New Jersey). FG 7142, provided by Drs. C. Braestrup and E. N. Petersen, A/S Ferrosan, Denmark, was suspended in distilled water with one drop of Tween 80 per 3.5 ml. The suspension was extensively sonicated and administered in a volume of 2 ml/kg, i.p. Animals were killed 30 min after FG 7142 administration, and various brain regions were dissected out as previously described [11]. Tissue DA and 3,4-dihydroxy-phenylacetic

acid (DOPAC) levels were determined by high pressure liquid chromatography with electrochemical detection [12].

RESULTS

FG 7142 administered at 5, 10, and 20 mg/kg i.p. for 30 min produced a dose-dependent increase in DA metabolite levels in the prefrontal cortex (Fig. 1). Doses of 10 mg/kg and 20 mg/kg, which have been found to be anxiogenic in rats [7] and in cats [8], caused significant increases in DOPAC levels over vehicle controls by 42 and 85% respectively. However, the mesocingulate DA system, which has been shown not to be activated by stress [10], exhibited no change in DOPAC levels after FG 7142 administration at all three doses.

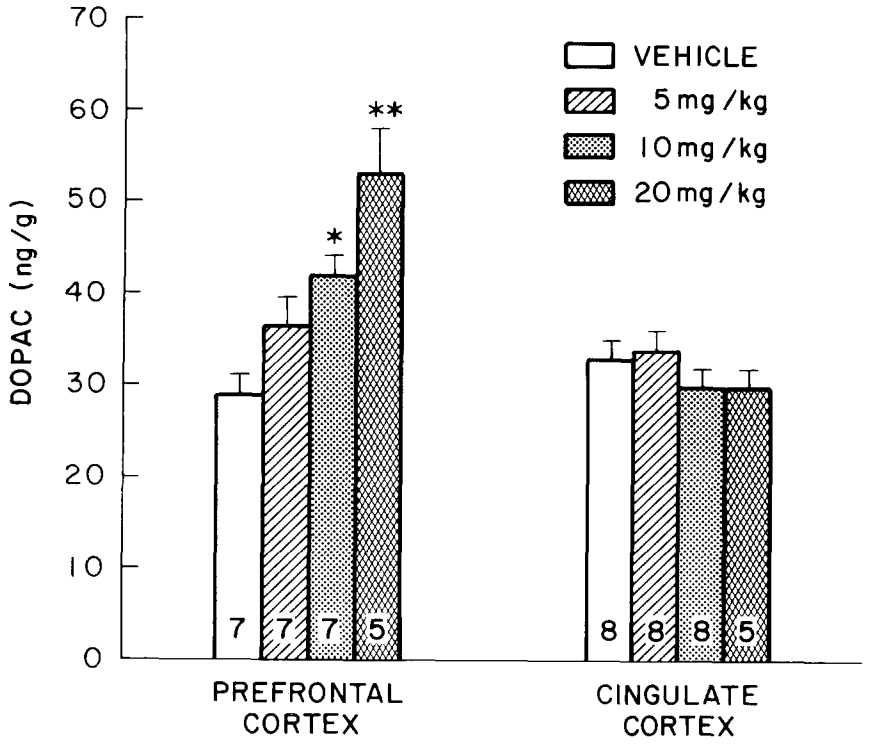

Fig. 1. Dose-response curve for the effects of FG 7142 on DOPAC levels in the mesocortical DA neurons. FG 7142 was administered i.p. 30 min before decapitation. Numbers in the columns refer to the number of individual animals. Results are expressed as the mean ± S.E.M.

* Differs significantly from vehicle controls ($P < 0.05$), by one-way analysis of variance using the Neuman-Keuls test.

** Differs significantly from vehicle controls and all other treatment groups ($P < 0.01$), by one-way analysis of variance using the Neuman-Keuls test.

The effects of FG 7142 on DOPAC levels in the mesopiriform (piriform cortex), the mesolimbic (olfactory tubercle), and the nigrostriatal (striatum) DA systems were also examined at doses of 5 mg/kg and 10 mg/kg

(Fig. 2). At 5 mg/kg, no effect of FG 7142 was seen on any of the DA systems examined, with the exception of the prefrontal cortex where a significant (26%) increase in DOPAC level was observed. At 10 mg/kg, DOPAC levels in both the olfactory tubercle and the striatum were decreased over vehicle controls by 21 and 19%, respectively, whereas the DOPAC level in the prefrontal cortex was significantly increased by 42%. At these two dosages there was no significant change in DA levels in any of the brain regions examined (data not shown).

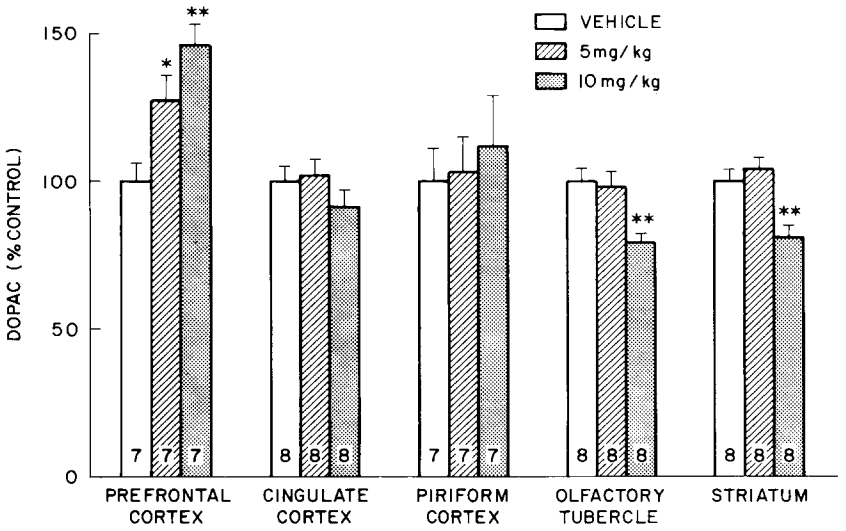

Fig. 2. Effects of FG 7142 on DOPAC levels in the mesocortical, mesolimbic and nigrostriatal DA systems. FG 7142 was administered i.p. 30 min before decapitation. Numbers in the columns refer to the number of individual animals. Values are presented as a percentage of control DOPAC levels. Data are expressed as the mean ± S.E.M.

* Differs significantly from vehicle controls ($P < 0.05$), by two-tailed Student's t-test.

** Differs significantly from vehicle controls and from 5 mg/kg ($P < 0.01$), by one-way analysis of variance using the Neuman-Keuls test.

DISCUSSION

In the present study, we have demonstrated that the beta-carboline FG 7142 selectively elevated DA metabolism in the prefrontal cortex in a dose-dependent manner. To our knowledge, this is the first report indicating that an anxiogenic benzodiazepine receptor "inverse" agonist selectively activates the mesoprefrontal DA system, a neuronal system which has been suggested to be involved in emotional stress. Moreover, this study confirms our previous finding of a benzodiazepine receptor modulation of this DA system. It is also of interest that a decrease in DA metabolism was observed in the striatum after FG 7142 (10 mg/kg)

treatment, suggesting an inhibition of the nigrostriatal DA system by this beta-carboline. This finding is in line with a recent observation that beta-carbolines increase the firing rate of zona reticulata (ZR) cells in the substantia nigra [13]. These gamma-aminobutyric acid (GABA) sensitive cells have been shown to exert an inhibitory influence on DA cells in the zona compacta (ZC) of the substantia nigra [14]. As the ZR cells are twenty times more sensitive to GABA than the ZC cells, FG 7142 may preferentially activate the ZR cells. An activation of the ZR cells could result in an inhibition of DA cells in the ZC that project to the striatum, and thus reduce DA metabolism in the striatum.

In summary, we find that the mesoprefrontal DA system, which has been shown to be selectively activated by stress, is likewise selectively activated by an anxiogenic benzodiazepine receptor ligand. This study thus provides evidence consistent with the involvement of the mesoprefrontal DA system in an endogenous benzodiazepine receptor modulation of the manifestation of anxiety.

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