Biochemical Pharmacology, Vol. 29, pp. 2895-2896

0006-2952/80/1015-2895 $02.00/0

EFFECT OF CHRONIC TREATMENT WITH ANTIDEPRESSANTS ON BETA-ADRENERGIC RECEPTOR BINDING IN GUINEA PIG BRAIN

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(Received 20 June 1980; accepted 23 July 1980)

In the rat cerebral cortex, catecholamine-stimulated accumulation of cyclic adenosine-3',5'-monophosphate (cyclic AMP) has been reported to be antagonized by both alpha- and beta-adrenergic blocking agents (1). In the guinea pig cerebral cortex, beta-adrenergic blocking agents have hardly any effect on epinephrine- and norepinephrine-stimulated adenylate cyclase activity (1-3). Clark et al. (4) also failed to detect beta-adrenergic binding sites using [^{3}H]-dihydroalprenolol (DHA) in the guinea pig cerebral cortex. These findings suggest that the effect of catecholamine on the cyclic AMP level in the guinea pig cerebral cortex is mediated primarily via interaction with alpha-adrenergic receptors. However, after a detailed study, Bylund (5) showed that the guinea pig cerebral cortex does have [^{3}H]-DHA binding sites, similar to those in the rat brain, which have the characteristics of a beta$_1$-adrenergic receptor.

Some in vitro experiments have indicated that the cerebral cortex of the rat and that of the guinea pig respond differently to antidepressant drugs with respect to accumulation of cyclic AMP (6-8). Thus, there appears to be species differences between guinea pig and rat brain in their response to beta-adrenergic agents and tricyclic antidepressants.

It also has been reported by several investigators that chronic treatment with antidepressant drugs causes a reduction in [^{3}H]-DHA binding sites in rat brain (9-13). Since the presence of [^{3}H]-DHA binding sites has been demonstrated, it was of interest to examine the effect of chronic antidepressant treatments on [^{3}H]-DHA binding in guinea pig cortex. Although we observed [^{3}H]-DHA binding characteristics of guinea pig cortex similar to those reported by Bylund (5), it would be interesting to determine whether there is a difference in the chronic effect of antidepressants on beta-adrenergic receptor binding in the guinea pig and rat brain. Contrary to the reports on the rat brain (9-14), our data show no significant change in beta-adrenergic receptor density or apparent affinity for [^{3}H]-DHA in the guinea pig cerebral cortex after chronic treatment with desipramine, phenelzine, or electroconvulsive shock (ECS).

Guinea pigs (200-250 g) were injected intraperitoneally with desipramine (10 mg/kg) or phenelzine (5 mg/kg) or were subjected to ECS (75 mA for 1 sec through transcorneal electrodes) once daily for 15 days. Control guinea pigs were injected with saline. The experimental procedures for the preparation of tissue homogenate and for the [^{3}H]-DHA binding assay were the same as described by Pandey et al. (11).

The maximal number of [^{3}H]-DHA binding sites (B_{max}) and the apparent dissociation constant (K_d) for guinea pig cerebral cortex were found to be 120 fmoles/mg protein and 2.41 nM respectively. These values are similar to those reported for guinea pig (5) and rat (10,11,14) cerebral cortex. The effects of chronic treatment of guinea pigs with tricyclic antidepressants (desipramine), monoamine oxidase

Table 1. Effect of chronic treatment with antidepressants on receptor density and dissociation constant of beta-adrenergic receptors in guinea pig cerebral cortex

Treatment	N	Receptor density (fmoles/mg protein)	Dissociation constant (nM)
Control	7	122 + 9	2.31 ± 0.44
Desipramine	7	114 ± 11*	2.41 ± 0.47*
Phenelzine	6	119 ± 10*	2.88 ± 0.34*
ECS	6	100 ± 5*	2.54 ± 0.49*

*Paired t-test showed no significant difference as compared to the control.

inhibitor (phenelzine) and electroconvulsive shock are shown in Table 1. The binding experiments were carried out with four different concentrations of [^{3}H]-DHA (0.4 to 3.2 nM) and data were analyzed by Scatchard plot. No significant change in either receptor density (B_{max}) or apparent affinity (K_d) was observed following chronic injection of desipramine or phenelzine. Although treatment with ECS caused a slight decrease in receptor density, this was not statistically significant (P value between 0.05 and 0.1).

In contrast to our findings in the guinea pig cortex, other investigators have reported that similar chronic antidepressant treatment of rats led to a reduction in beta-adrenergic receptor density (9-14). These observations suggest that there seems to be species differences between guinea pig and rat cerebral cortex in the response of beta-adrenergic receptors to chronic antidepressant treatment. Whether these differences are due to a difference in the membrane structure or in the beta-receptor coupled adenylate cyclase complex of adrenergic neurons remains to be investigated.

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