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Differential Effects of Olfactory Bulbectomy on $GABA_A$ and $GABA_B$ Receptors in the Rat Brain

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DENNIS, T., V. BEAUCHEMIN AND N. LAVOIE. *Differential effects of olfactory bulbectomy on $GABA_A$ and $GABA_B$ receptors in the rat brain.* PHARMACOL BIOCHEM BEHAV **46**(1) 77–82, 1993.—GABAergic mechanisms have been implicated in the bilateral olfactory bulbectomy (OBX) animal model of depression, where $GABA_B$ receptor binding sites have been shown to decrease markedly at specific time points after OBX. However, as no detailed time course of events has been determined, the present study investigated the effects of OBX on high-affinity $GABA_A$, $GABA_B$, β-adrenergic, and benzodiazepine receptor binding parameters in membrane preparations from rat brain regions at weekly intervals (1–4 weeks) after OBX. Persistent significant increases (40–60%) in B_{max} values of high affinity $GABA_A$ receptors were observed in the frontal cortex throughout the period investigated following OBX. B_{max} values in the hippocampus increased significantly after 1 week (53%) but were not statistically significant thereafter. No changes in $GABA_A$ binding parameters were observed in the hypothalamus or cerebellum. Conversely, $GABA_B$ receptor densities were significantly decreased in the frontal cortex after 1 (−38%) and 2 (−41%) weeks and moderately decreased 3 and 4 weeks (−27 and −23%, respectively) after OBX, while in the cerebellum they were significantly increased after 1 week (96%) and returned to sham-operated levels by 3 weeks. No changes in $GABA_B$ receptor binding parameters were observed in the hippocampus or hypothalamus. Binding parameters for benzodiazepine receptor binding sites or β-adrenoceptors were not modified throughout the time course. GABAergic transmission, reflected by changes in $GABA_A$ and $GABA_B$ receptor density in the frontal cortex, may be altered in OBX rats. The persistence of the change in $GABA_A$ receptor density, contrasting with the transient change in $GABA_B$ receptors, suggests that the former, rather than the latter, is more likely to be related to the long-lasting behavioral deficits induced by OBX.

$GABA_A$ receptors $GABA_B$ receptors Benzodiazepine receptors β-Adrenergic receptors
Olfactory bulbectomy Rat brain

ANIMAL models of depression have long been a subject of controversy. These models range from simple screening tests for potential antidepressant treatments to the induction of depressive-like symptoms. One of the models that can be useful in the study of the neurobiological substratum of depression and the mechanisms of action of antidepressant treatments is the bilateral olfactory bulbectomy (OBX) model (12,34). Following OBX, rats display antidepressant-reversible behavioral and biochemical changes that find their correlates in depressed patients (4,5,12,15,31).

A number of studies following OBX have shown that noradrenaline turnover in the amygdaloid cortex and forebrain in general is decreased, while that of GABA is increased (9,21). In line with such changes, β-adrenoceptors were reportedly increased in the pons and hippocampus; however, this appears to be due to an increase in binding affinity rather than a change in binding density (11,29). Moreover, α_2-adrenoceptors are increased in the forebrain but not in the olfactory cortex of OBX rats (8,21). That $GABA_B$ binding densities are decreased in the frontal cortex both in the OBX model (13,16,17), 2 and 4 weeks after bulb ablation, and in the learned helplessness model (20) would implicate GABAergic mechanisms in these animal models of depression. Consistent with such a notion, Lloyd et al. (18,24) have shown increased $GABA_B$ receptor binding in the rat frontal cortex following long-term administration of different types of antidepressant treatments including GABAmimetic or electroconvulsive shock treatments. This upregulation in $GABA_B$ binding appears to be specific for antidepressants as other psychotropic drugs, for example, haloperidol, chlorpromazine and diazepam, are inactive, while phenobarbital, diphenylhydantoin, and reserpine downregulate $GABA_B$ receptors (17). Moreover,

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desipramine-induced reversal of a stepdown passive avoidance deficit appears to be associated with increases in $GABA_B$ receptor binding (13).

The above-mentioned studies (13,16,17) found decreased $GABA_B$ receptor binding at specific time points after OBX; however, a detailed time course of possible variations in density of both $GABA_A$ and $GABA_B$ receptors following OBX has not been determined. Given that receptor binding levels determined from a single concentration of radioligand cannot define whether variations are related to changes in affinities (K_d) or maximal binding capacities (B_{max}), the present study investigated the binding parameters of the high-affinity $GABA_A$, $GABA_B$, β-adrenergic, and benzodiazepine (BDZ) receptor binding sites 1, 2, 3, and 4 weeks after bilateral OBX.

METHOD

Animals, Drugs, and Chemicals

Male Sprague–Dawley rats, 230–250 g, were obtained from Charles River Canada (St. Constant, Quebec). Before and after surgery, animals were housed in groups of four and maintained on a 12 L : 12 D cycle (light on at 0700 h) in a temperature- and humidity-controlled room, with standard laboratory chow and water ad lib.

Drugs and chemicals were obtained from the following sources: GABA (35–80 Ci/mmol) and (−)-[^{3}H]CGP-12177 (38 Ci/mmol) from Amersham Canada (Oakville, Ontario); [methyl-^{3}H]flunitrazepam (84 Ci/mmol) from DuPont Canada (Mississauga, Ontario); isoguvacine and (±)baclofen from Research Biochemicals, Inc. (Natick, MA); GABA and propranolol from Sigma Chemical Co. (St. Louis, MO); all other reagents were of analytic grade and obtained from Fisher Scientific (Montréal, Quebec).

CL-218,872 was generously donated by Dr B. Beer, American Cyanamid (Pearl River, NY); PK-11195 (RP-52028) was a gift from Dr J.C. Blanchard, Rhône-Poulenc (Vitry-sur-Seine, France); Ro 15-1788 (flumazenil) was a gift from Hoffman-LaRoche (Etobicoke, Ontario).

Surgery

Olfactory bulbectomy was carried out as previously described (10). Rats were anesthetised (chloral hydrate, 350 mg/kg, IP) and mounted in a stereotaxic frame (Kopf Instruments, Topanga, CA). Following a skin incision, bilateral burr holes were made in the skull surface. The dura was pierced and olfactory bulbs sectioned and aspirated; the remaining cavities were filled with haemostatic sponge. The incision was sprayed with antibiotic and closed with wound clips. Sham-lesioned rats were similarly operated but the bulbs were left intact. Animals were sacrificed by decapitation without anesthetic 1, 2, 3, and 4 weeks after surgery. Brains were quickly removed and inspected macroscopically. Brains were discarded if any residual tissue of the main olfactory bulbs remained or if the frontal cortex had been damaged during the surgical procedure. The frontal cortex (including prefrontal and frontoparietal motor cortex), hypothalamus, hippocampus, and cerebellum were rapidly dissected, frozen individually in dry ice, and stored at −80°C.

Membrane Binding Procedures

All brain tissue samples removed from individual rats were assayed separately. The membrane binding procedures used were previously described elsewhere. Binding parameters for $GABA_A$ and $GABA_B$ receptors were determined in the presence of 100 μM baclofen or 40 μM isoguvacine, respectively, using the method of Hill et al. (6). The range of [^{3}H]GABA concentrations used was 3–300 nM in both cases; specific binding was defined with 100 μM GABA or baclofen, respectively. [^{3}H]Flunitrazepam binding parameters (concentration range 0.1–10 nM) were determined using a modified procedure of Suranyi-Cadotte et al (28). In these analyses, 1 μM PK 11195 was added to the incubation buffer to mask peripheral BDZ receptors. This was deemed necessary as peripheral BDZ receptors have been shown to increase dramatically following brain lesions (1,2). BDZ_1 and BDZ_2 populations were estimated by incubation of membranes with 1 nM [^{3}H]flunitrazepam in the presence and absence of 200 nM CL-218,872 as described by Lo et al. (19); 2 μM Ro 15-1788 defined specific binding for these assays. β-Adrenoceptor binding parameters were determined with the procedure of Riva and Creese (27) using (−)-[^{3}H]CGP-12177 as radioligand with concentrations ranging from 0.02–2 nM; specific binding was defined with 10 μM propranolol.

Statistics

Binding data were analyzed by nonlinear regression analysis using the Receptor Fit Saturation Two-Site software package (Lundon Software, Chagrin Falls, OH). Values are expressed as means ± SEM. Statistical analyses were performed using analysis of variance (ANOVA) followed by Duncan's test for multiple comparisons, for which the level of significance was fixed at $p < 0.05$.

RESULTS

Analyses for the binding parameters of the four ligands and structures investigated were carried out using tissues from OBX rats and their corresponding sham-operated controls. In all cases, there were no significant differences (ANOVA) in K_d or B_{max} values between control groups from each time point; thus, these values were pooled. The maximal binding capacities (B_{max}) of $GABA_A$ receptors increased in the frontal cortex by 1 week (38%) following OBX and reached statistical significance at 2 weeks (49%). This augmentation persisted throughout the study (54 and 60% after 3 and 4 weeks, respectively) and was not accompanied by any change in K_d values (Fig. 1A). B_{max} values were also increased significantly in the hippocampus after 1 week (53%) but were not significantly different thereafter (Fig. 1A). No changes in $GABA_A$ binding parameters were seen in the hypothalamus or cerebellum (Fig. 1A). K_d values in the cortex, hippocampus, hypothalamus, and cerebellum were 50.0 ± 4.0, 48.0 ± 5.1, 43.3 ± 3.3, and 66.4 ± 9.0 nM, respectively.

Despite the observed variations in $GABA_A$ binding densities in the frontal cortex, these increases were not accompanied by any parallel changes in total BDZ receptor binding densities (Table 1). Indeed, no significant changes in [^{3}H]flunitrazepam binding parameters were observed in any of the structures investigated throughout the study (Table 1). Moreover, no variations in BDZ_1 or BDZ_2 subtype populations were seen (data not shown).

In contrast, decreases in $GABA_B$ receptor binding densities with no change in K_d values were observed in the frontal cortex (Fig. 1B). B_{max} values were significantly decreased by 38 and 41% 1 and 2 weeks after OBX, respectively. However, even though binding densities were still found to be 27 and 23% lower than sham-operated control levels at 3 and 4 weeks, respectively, these decreases were no longer statistically signif-

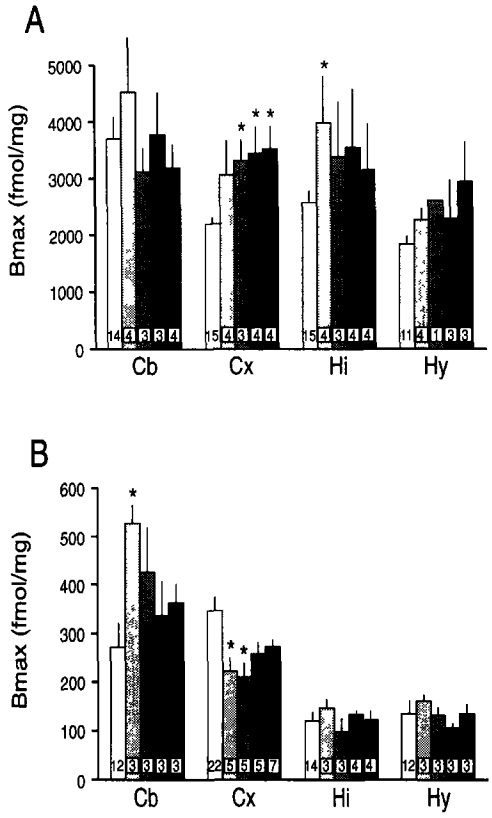

FIG. 1. Time course of the effects of bilateral olfactory bulbectomy (OBX) on B_{max} values (fmol/mg protein) of: (A) specific high-affinity $GABA_A$ reptors and (B) specific high-affinity $GABA_B$ receptors. Experiments were performed as described in the Method section. Results represent the means ± SEM of data obtained from duplicate determinations from n animals, indicated at the foot of each column. In all cases, the first and subsequent columns represent sham-operated animals followed by OBX at 1, 2, 3, and 4 weeks, respectively. K_d values were not significantly changed at any time in any of the structures investigated. Cb, cerebellum; Cx, frontal cortex; Hi, hippocampus; Hy, hypothalamus. $^*p < 0.05$.

icant (Fig. 1B). B_{max} values in the cerebellum increased by 96% after 1 week and returned to normal levels by 3 weeks (Fig. 1B). $GABA_B$ binding parameters in the hippocampus and hypothalamus were not altered at any time following OBX (Fig. 1B). K_d values in the cortex, hippocampus, hypothalamus, and cerebellum were 47.5 ± 3.9, 52.2 ± 5.4, 53.7 ± 5.9, and 43.4 ± 5.8 nM, respectively.

Binding parameters for [^{3}H]CGP-12177 binding to β-adrenoceptors in the frontal cortex or hippocampus were not modified throughout the time period investigated following OBX (Table 1).

DISCUSSION

The results of the present study show that, over the time period investigated, persistent significant increases in $GABA_A$ receptor binding densities, with no change in K_d, are observed in the frontal cortex following OBX. Conversely, during the first 2 weeks following surgery cortical $GABA_B$ binding densities are significantly decreased. However, these decreases in B_{max} values show a gradual tendency to normalize and are no longer statistically significant 3 and 4 weeks after OBX.

The present results confirm and extend the previous reports on $GABA_B$ binding of Lloyd et al. (13,16,17). Indeed, the results of our study show good agreement in the variations of $GABA_B$ binding at the time points (14 and 29 days) chosen by the previous authors (13,16,17). In the present study, B_{max} values for $GABA_B$ receptors in the rat frontal cortex are significantly decreased by 40% compared to sham-operated controls both 1 and 2 weeks after OBX, comparable to the 40–50% decrease observed after 2 weeks by Lloyd (16,17). Variations in cerebellar $GABA_B$ receptor densities are similar after 2 weeks, but our study shows a marked, transient increase after 1 week that tends to normalize. Moreover, confirming their previous observations (16,17), no changes were observed in the hippocampus in the present study. In addition, 4 weeks after OBX we still observed a 23% reduction in $GABA_B$ binding in the cortex whereas the previous authors (13) reported a 27% decrease using a single concentration of radioligand. The fact that the decrease in $GABA_B$ binding we observed 4 weeks after OBX was not statistically significant while theirs was (13) after 29 days may be explained by the large population of animals used in their study. Importantly, our results suggest that, over the time period studied, $GABA_B$ receptor densities tend to normalize. These observations are of critical importance to the GABA hypothesis of antidepressant drug action as proposed by Lloyd (18,24). The study of Joly et al. (13) suggests that upregulation of cortical $GABA_B$ receptor density following prolonged treatment with desipramine is associated with a normalization of the behavioral deficit in a stepdown passive avoidance paradigm. However, cortical $GABA_B$ binding levels in the desipramine-nonresponding group were also normalized in their study (13). Further, the trend toward a normalization of $GABA_B$ receptor binding densities with time observed in the present study is consistent with that seen in the various studies performed by these authors (13, 16,17). Thus, as behavioral deficits persist (10,13) while $GABA_B$ binding densities tend to normalize, it would appear that $GABA_B$ receptor density normalization is not the sole requisite to reverse the deficit in stepdown passive avoidance behavior.

As for the other regions studied, a transient increase in $GABA_A$ B_{max} values was observed in the hippocampus 1 week after bulb ablation. In the hypothalamus and cerebellum, no changes in $GABA_A$ binding parameters were observed. In addition, no changes in BDZ binding parameters were noted in any of the structures studied (Table 1). This observation is consistent with the results of Hirsch (7), who found no change in [^{3}H]diazepam binding 16 weeks after OBX. However, one may have expected an increase in [^{3}H]flunitrazepam binding in the frontal cortex parallel to that of $GABA_A$ receptors. There are a number of possible explanations as to why this was not the case. In a recent study, Weizman et al. (33) pointed out that measurements of variations in BDZ binding parameters can yield differing results between in vitro and in vivo conditions. These authors suggest that in vivo binding may be a more precise reflection of receptor changes (33). Second, the present binding studies were carried out on membrane preparations. This may mask discrete regional changes that could perhaps be detected using autoradiographic procedures; such experiments are presently being carried out in our laboratory. Finally, it is generally accepted that high-affinity $GABA_A$ receptors are not linked to BDZ binding sites (30), and in the present study only high-affinity [^{3}H]$GABA_A$ binding was measured. Thus, this would suggest that bulbectomy results in an upregulation of cortical high-affinity $GABA_A$ receptor binding sites that are not associated with BDZ recep-

TABLE 1

REGIONAL SATURATION ANALYSIS OF RADIOLIGAND BINDING TO MEMBRANE PREPARATIONS OF THE RAT BRAIN AT DIFFERENT TIMES FOLLOWING OBX

	Control		OBX (weeks)							
			1		2		3		4	
	K_d (nM)	B_{max} (fmol/mg)	K_d (nM)	B_{max} (fmol/mg)	K_d (nM)	B_{max} (fmol/mg)	K_d (nM)	B_{max} (fmol/mg)	K_d (nM)	B_{max} (fmol/mg)
BZD										
Cb	1.72 ± 0.08 (12)	1,043 ± 54	1.73 ± 0.14 (3)	1,041 ± 24	1.87 ± 0.17 (3)	1,247 ± 285	1.60 ± 0.22 (3)	942 ± 244	1.51 ± 0.13 (3)	1,555 ± 292
Cx	1.35 ± 0.05 (16)	2,044 ± 73	1.56 ± 0.07 (4)	2,291 ± 201	1.43 ± 0.10 (4)	2,057 ± 252	1.32 ± 0.08 (4)	2,030 ± 144	1.29 ± 0.05 (4)	2,059 ± 162
Hi	1.27 ± 0.04 (12)	1,701 ± 69	1.53 ± 0.08 (3)	1,835 ± 149	1.30 ± 0.09 (3)	1,610 ± 83	1.23 ± 0.12 (3)	1,651 ± 130	1.37 ± 0.07 (3)	1,744 ± 141
Hy	0.94 ± 0.02 (12)	1,198 ± 74	1.12 ± 0.01 (3)	1,361 ± 112	1.02 ± 0.09 (3)	1,216 ± 77	0.85 ± 0.13 (3)	1,137 ± 153	0.93 ± 0.04 (4)	1,124 ± 139
β-Adrenoceptor										
Cx	0.08 ± 0.01 (15)	64 ± 2	0.09 ± 0.02 (4)	64 ± 7	0.10 ± 0.01 (3)	61 ± 3	0.08 ± 0.01 (3)	62 ± 4	0.07 ± 0.01 (5)	62 ± 3
Hi	0.10 ± 0.01 (12)	31 ± 2	0.08 ± 0.01 (3)	28 ± 1	0.09 ± 0.01 (3)	28 ± 3	0.10 ± 0.01 (2)	30 ± 4	0.11 ± 0.02 (4)	37 ± 5

Animals were sacrificed 1, 2, 3, and 4 weeks after OBX. Experiments were performed as described in the Method section. Results represent the means ± SEM of data obtained from duplicate determinations from *n* animals, indicated in parentheses. B_{max} values are expressed as fmol/mg protein. Cb, cerebellum; Cx, frontal cortex; Hi, hippocampus; Hy, hypothalamus.

tors. Moreover, this effect is unlikely to be a consequence of postoperative stress. Physical and psychological stress will result in rapid cerebral and plasmatic elevations of neuroactive steroids that are highly potent allosteric modulators of $GABA_A$ receptors (23,26). However, various stressors have been shown to decrease in vivo [^{3}H]Ro 15-1788 binding in the cortex but also to increase mRNAs for α_1- and γ_2-subunits of $GABA_A$ receptors and low-affinity $GABA_A$ binding densities (3,14,25,32). Thus, the fact that stress primarily affects $GABA_A$/BDZ receptors lends further support to the notion that the upregulation of high-affinity $GABA_A$ receptors in the frontal cortex observed in the present study is a consequence of OBX and not stress effects.

Jesberger and Richardson (11), using [^{3}H]dihydroalprenolol, reported an increase in β-adrenoceptor binding in the hippocampus of OBX rats 7 weeks after surgery. In a more recent study, this increase in binding was further characterized using [^{125}I]iodocyanopindolol and shown to be the result of a 30% increase in affinity with no change in B_{max} values (29). This increased affinity was observed both in the hippocampus and amygdala, but not in the cerebral cortex, and was proposed to result from an increased coupling of the receptors with G proteins (29). In the present study, we confirmed a lack of significant variations in the binding parameters of [^{3}H]CGP-12177 to β-adrenoceptors in the cortex. However, there was no change in the affinity of this ligand in the hippocampus either. Thus, our results do not corroborate these previous observations (29). This discrepancy may be due to methodological differences, that is, the radioligand used rather than the time points investigated. Although [^{3}H]CGP-12177 displays high affinity for β-adrenoceptors (0.10 nM in our hands), [^{125}I]iodocyanopindolol has 5- to 10-fold greater affinity (22,29) but is less selective and demonstrates high affinity toward 5-hydroxytryptamine$_{1B}$ (5-HT_{1B}) receptors (22). In light of the small change in affinity observed by the previous authors (29), it is possible that the use of [^{3}H]CGP-12177 in the present study may have precluded the detection of such a change.

In conclusion, following OBX persistent significant increases in high-affinity $GABA_A$ receptor binding site densities were observed in the frontal cortex throughout the time period studied. Conversely, in the same region $GABA_B$ receptor binding site densities were significantly decreased 1 and 2 weeks after surgery and more moderately so after 3 and 4 weeks. These changes in GABA receptor densities are likely to result in or from alterations of GABAergic neurotransmission. The fact that cortical $GABA_B$ receptor densities tend to normalize with time while increased $GABA_A$ binding densities persist would suggest that the upregulation of $GABA_A$ receptors, rather than the downregulation of $GABA_B$ receptors, might underlie the behavioral deficits elicited by OBX.

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