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Effects of Bulbectomy and Subsequent Antidepressant Treatment on Brain 5-HT_2 and 5-HT_{1A} Receptors in Mice

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GUREVICH, E. V., I. A. ALEKSANDROVA, N. A. OTMAKHOVA, Y. A. KATKOV, I. V. NESTEROVA AND N. V. BOBKOVA. *Effects of bulbectomy and subsequent antidepressant treatment on brain 5-HT_2 and 5-HT_{1A} receptors in mice.* PHARMACOL BIOCHEM BEHAV **45**(1) 65–70, 1993.—The effects of bilateral olfactory bulbectomy on serotonergic 5-HT_2 and 5-HT_{1A} receptor binding were studied in the frontal cortex (FC), limbic structures (LS), including the hippocampus, amygdala, olfactory tubercule, and piriform cortex, and hypothalamus (HTH) in mice. Bulbectomy resulted in the increase of B_{max} for [^{3}H]spiperone binding with 5-HT_2 receptors in FC in C57Bl/6j. The receptors in LS and HTH remained unchanged. Subchronic treatment of the bulbectomized mice with antidepressant trazodone (20 mg/kg/day, IP, 14 days) induced downregulation of 5-HT_2 receptors in FC and LS. The other two antidepressants used, amytriptyline (20 mg/kg/day, IP, 14 days) and imipramine (10 mg/kg/day, IP, 14 days), did not alter these receptors. [^{3}H]8-OH-DPAT binding with 5-HT_{1A} receptors was not altered by bulbectomy in any brain area in C57Bl/6j mice. Amitriptyline and trazodone decreased B_{max} for these receptors in FC in the bulbectomized mice while imipramine was ineffective. Amitriptyline and imipramine significantly increased B_{max} and decreased K_d in HTH, and trazodone displayed the same tendency. Bulbectomy did not alter 5-HT_2 receptors in DBA/2j mice. Amytriptyline increased K_d in the all brain areas without changing B_{max} in the bulbectomized DBA/2j mice. Trazodone significantly decreased B_{max} in FC and increased K_d in FC and LS. Imipramine decreased B_{max} while increasing K_d in LS. The possible involvement of the serotonin receptor subtypes in the bulbectomy-induced behavioral deficits and in the restorative action of the antidepressants is discussed.

Binding study 5-HT_2 receptors 5-HT_{1A} receptors Frontal cortex Limbic area Hypothalamus
Bulbectomy C57Bl/6j mice DBA/2j mice

THE serotonergic system is generally believed to be involved in both the pathogenesis of depression and in the mechanisms of antidepressant action. Endogenous depression has been shown to be accompanied by 5-hydroxytryptamine$_2$ (5-HT_2) receptors supersensitivity in blood platelets (7,29), as well as in brain tissue (2,49). Different antidepressants have been shown to downregulate 5-HT_2 receptors (11,12,24,32,36, 38,43) and the associated process of 5-HT-stimulated IP3 generation (32,43) in the rat brain. 5-HT_{1A} receptors also seem to play an important role in the pathophysiology of depression as well as in antidepressant action. 5-HT_{1A} agonists have been proven effective in the treatment of nonmelancholic depressive patients (42). They have also been shown to eliminate the escape deficit in the learned helplessness situation, the behavioral paradigm sensitive to antidepressant treatment (16). The stimulation of 5-HT_{1A} receptors as well as the blockade of 5-HT_2 receptors appear to lead to an antidepressant-like effect in the differential-reinforcement-of-low-rate paradigm (28). Antidepressant treatment reduced 8-OH-DPAT-induced hypothermia, a 5-HT_{1A}-mediated presynaptic response, in both mice and rats (18,19). In rats, postsynaptic serotonin syndrome induced by 8-OH-DPAT was also reduced by the same treatment. Chronic treatment with imipramine has been shown to reduce the number of postsynaptic 5-HT_{1A} receptors in the rat frontal cortex and hippocampus (30). Antidepressants have been shown to decrease the degree of 5-HT_{1A} receptor-mediated inhibition of adenylate cyclase in the rat hippocampus, an effect similar to that of 5-HT_{1A} agonists (33).

These data suggest that 5-HT_2 and 5-HT_{1A} receptors are involved in the pathogenesis of depression and in the action of antidepressant drugs. With the exception of postmortem examination of the brain tissue, it is impossible to study the

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receptor functions in the CNS of depressive human patients. The majority of the data concerning the receptor mechanisms of antidepressant action were obtained using normal animals chronically treated with antidepressants. But, it has been shown that neurochemical (44) as well as behavioral (22) consequences of antidepressant treatment can differ substantially in normal and depressive subjects. It seems more appropriate to use animal models of depression to investigate the receptor functions in depression as well as the receptor mechanisms of antidepressant action.

Bulbectomized rats have been shown to exhibit several behavioral deficits corrected by chronic antidepressant treatment (5,6,9,14,22) and are considered as an animal model of depression (39,48). The neurochemical mechanisms underlying the behavioral deficits in bulbectomized animals are far from clear. Bulbectomy is thought to cause the behavioral deficits, at least in part, through the alteration of the serotonergic system in different brain regions. Drugs that increase serotonergic transmission were able to decrease passive avoidance deficit caused by bulbectomy (5,23). The infusion of antidepressant drugs potentiating serotonergic transmission (or serotonin agonists) into the medial amygdala improved passive avoidance in bulbectomized rats (6,14,26). The serotonin antagonist metergoline administered systemically or into the medial amygdala blocked the effects of antidepressants on passive avoidance in bulbectomized rats (5,14,23). Destruction of serotonergic terminals in the olfactory bulbs by intrabulbar injection of 5,7-dihydroxytryptamine produced a deficit in passive avoidance similar to that caused by bulbectomy, while the destruction of catecholaminergic neurons did not (9). Bulbectomy decreased platelet serotonin uptake rate and increased synaptosomal uptake rate; both effects were reversible by chronic antidepressant treatment (8). Because it is known that the dorsal raphe nucleus, the point of origin for serotonin projections to limbic and forebrain regions, has input to olfactory bulbs (1), it seems likely that disruption of these connections as the result of bulbectomy can change serotonergic transmission in raphe nucleus and other brain regions connected to it.

Recently, we demonstrated that bulbectomized C57Bl/6j mice exhibited the behavioral syndrome close to that found in bulbectomized rats, which was reversed by chronic treatment with several clinically active antidepressants (35). Now, we studied the effects of bulbectomy on brain 5-HT_2 or 5-HT_{1A} receptors in mice as well as the effect of chronic antidepressant treatment on these serotonin receptor types in bulbectomized mice.

METHOD

Animals

Male C57Bl/6j and DBA/2j mice weighting 25–30 g at the time of surgery (approximately 2 months old) were used in these experiments. All animals were kept at constant temperature of 22 ± 1°C and under a 12 L : 12 D cycle. They were housed in groups of five animals and received food and water ad lib.

Surgery and Drugs

The surgery was described in detail elsewhere (35). In short, mice were anesthetized with 0.2–0.4 ml 100 mg/ml ketamine solution. Olfactory bulbs were removed by gentle aspiration through the hole in the skull. Sham-operated mice were treated identically except the bulbs were not removed. Antidepressant treatment started 2 weeks after bulbectomy. The following drugs were used: amitriptyline HCl (AM) (20 mg/kg), trazodone (TZ) (20 mg/kg), and imipramine HCl (IM) (20 mg/kg). All drugs were dissolved in normal saline and administered IP in 0.25 ml. Sham-operated (SO) and control bulbectomized (BE) mice received saline injections. All drugs and vehicle were injected once a day for 14 consecutive days. Mice were killed by cervical dislocation 28 days after surgery and 4 h after the last drug injection. Animals with incomplete removal of olfactory bulbs or with frontal cortex damage were discarded.

Receptor Binding Assay

After decapitation, a mouse brain was promptly removed and the frontal cortex (FC), limbic structures (LS), and hypothalamus (HTH) were isolated. The FC included cortical tissue dissected from the anterior half of the convecsital part of each hemisphere. The LS and HTH were isolated using (21) as a guide. LS included the olfactory tubercles, lateral olfactory tract, piriform cortex, amygdala, and hippocampus. Pooled brain tissues from three to six mice were used for one saturation curve. Tissue was homogenized in 100 volumes of 0.05 M Tris-HCl, pH 7.4. The homogenate was centrifuged for 20 min at 40,000 × g at 4°C. The supernatant was discarded and the pellet was washed three times with the same volume of 0.05 M Tris-HCl. The final pellet was resuspended in either 40 or 80 volumes of the same buffer for subsequent determination of [^{3}H]spiperone or [^{3}H]8-OH-DPAT binding, respectively.

[^{3}H]Spiperone HCl (specific activity 69.4 Ci/mmol, Amersham, England) was used for the determination of 5-HT_2 receptors according to the method described by Peroutka and Snyder (37), with some modifications. The assay consisted of 800 μl membrane suspension (the equivalent of 20 mg wet tissue, or approximately 0.8–0.9 mg protein), 100 μl appropriate [^{3}H]spiperone solution, and 100 μl 0.05 M Tris-HCl, pH 7.4. Nonspecific binding was determined in the presence of cyprogeptadine (100 μM final concentration). Ten ligand concentrations, ranging from 0.5–5 nM, were used for each saturation curve.

[^{3}H]8-OH-DPAT (specific activity 234 Ci/mmol, Amersham) was used for the determination of 5-HT_{1A} receptors. The assay consisted of 800 μl membrane suspension (the equivalent of 10 mg wet tissue, or 0.4–0.5 mg protein), 100 μl [^{3}H]8-OH-DPAT solution, and 100 μl 0.05 M Tris-HCl, pH 7.4. Nonspecific binding was determined in the presence of 10 μM serotonin. Ten ligand concentrations, ranging from 0.2–3 nM, were used for each saturation curve.

Assays were incubated for 10 min at 37°C for 5-HT_2 receptors or for 30 min at 30°C for 5-HT_{1A} receptors. Assays were then transferred to the ice bath and rapidly filtered through the glass fibers filters (GF/C, Whatman, Clifton, NJ). The filters were washed four times with 5 ml ice-cold 50 mM Tris-HCl, pH 7.4, and transferred to the vials containing 5 ml scintillation fluid based upon dioxane (GS-8, Russia). Vials were allowed to stay for 1 h and then were counted with 40% efficiency. All measurements were performed in duplicate. Nonspecific binding was 40–55% for 5-HT_2 receptors and 15–20% for 5-HT_{1A} receptors. B_{max} and K_d were calculated from Scatchard plots. Protein was determined using the method of Bradford (3).

Data Analysis

Scatchard plots were analyzed using linear regression function in the STATGRAFICS statistical package (EXEC * U *

TABLE 1

[^{3}H]SPIPERONE BINDING IN SEVERAL BRAIN REGIONS IN C57Bl/6j MICE: EFFECTS OF BULBECTOMY AND ANTIDEPRESSANT TREATMENT

	Frontal cortex			Limbic area			Hypothalamus		
Group	B_{max}	K_d	n	B_{max}	K_d	n	B_{max}	K_d	n
Sham operated	894 ± 134	2.2 ± 1.1	6	664 ± 100	1.0 ± 0.2	5	584 ± 95	1.0 ± 0.2	5
Bulbectomized	1422 ± 134*	2.8 ± 0.6	6	597 ± 119	1.4 ± 0.2	5	491 ± 100	1.1 ± 0.2	5
BE+AM	1228 ± 132	3.3 ± 0.6	5	452 ± 49	2.4 ± 0.2†	5	363 ± 58	1.3 ± 0.2	5
BE+TZ	584 ± 44‡	1.0 ± 0.1†	6	289 ± 13†	1.4 ± 0.4	5	334 ± 41	0.9 ± 0.2	5
BE+IM	1196 ± 40	1.5 ± 0.1	5	576 ± 80	1.7 ± 0.3	5	534 ± 86	0.8 ± 0.1	5

B_{max} (fmol/mg protein) and K_d (nM) values are means ± SEM of n Scatchard plots. BE+AM, BE+TZ, and BE+IM represent the groups of bulbectomized mice treated with amitpiptyline, trazodone, and imipramine, respectively.
*$p < 0.05$ to sham-operated group; †$p < 0.05$ and ‡$p < 0.01$ to bulbectomized group according to Student's two-tailed t-test.

STAT, Version 2.1) on an IBM PC/AT. Comparisons of means were made with Student's two-tailed t-test.

RESULTS

The analysis of the Scatchard plots for the binding of [^{3}H]spiperone and [^{3}H]8-OH-DPAT revealed the presence of the only one high-affinity binding site for each ligand in all brain regions studied after all treatments used (data not shown).

In C57Bl/6j mice, bulbectomy increased B_{max} for 5-HT$_2$ receptors in the FC without changing K_d. Neither B_{max} nor K_d differed significantly in BE mice from SO controls in the other two brain areas studied, the LS and HTH (Table 1). Among the antidepressants used, only trazodone significantly altered these receptors: It decreased both B_{max} and K_d in the FC and decreased B_{max} in the LS.

Neither B_{max} nor K_d for 5-HT$_{1A}$ receptors was significantly altered by bulbectomy in any of the brain structures in C57Bl/6j mice (Table 2). Amitriptyline decreased B_{max} in the FC and increased B_{max} while decreasing K_d in the HTH. Trazodone also decreased 5-HT$_{1A}$ receptors density in the FC without significantly altering it in the two other brain areas, although it tended to increase B_{max} and decrease K_d in the HTH. Imipramine did not change B_{max} in the FC but, like amitryptiline, increased B_{max} and decreased K_d in the HTH.

Bulbectomy did not significantly alter 5-HT$_2$ receptors in DBA mice (Table 3). Amitriptyline increased K_d in all brain areas studied, without changing B_{max}. Trazodone significantly decreased B_{max} in the FC and increased K_d in the FC and LS. Imipramine decreased B_{max} while increasing K_d in the LS.

DISCUSSION

In the previous article, we demonstrated that bulbectomy in C57Bl/6j mice produced the depression-like behavioral syndrome, similar to that found in rats and similarly corrected by chronic antidepressant treatment (35). Our present data indicate that bulbectomy increased the density of 5-HT$_2$ receptors in the FC in C57 mice while the receptors in the LS and HTH remained unchanged. It is somewhat surprising because the cerebral cortex, in contrast to the limbic structures, apparently has no close connections with the olfactory bulbs (10, 25,27). Therefore, we expected to find the receptor alterations first and foremost in the limbic structures. It has been shown that the amygdala plays an important role in the bulbectomy-induced behavioral deficits (6,14). In the earlier study, both the transient and persistent changes in the opiate and muscarinic cholinergic receptor binding have been found in the amygdala and the other limbic areas (21). The alterations of β-adrenoreceptors have been found in the rat amygdala and hippocampus but not in the cerebral cortex (45). We included the frontal cortex in the present study mostly because the cortical 5-HT receptors are known to be sensitive to antidepressant treatment (11,32,36,43,41). However, the present data show that the bulbectomy-induced neurochemical

TABLE 2

[^{3}H]8-OH-DPAT BINDING IN BRAIN REGIONS OF C57Bl/6j MICE: EFFECTS OF BULBECTOMY AND ANTIDEPRESSANT TREATMENT

	Frontal cortex			Limbic area			Hypothalamus		
Group	B_{max}	K_d	n	B_{max}	K_d	n	B_{max}	K_d	n
Sham operated	162 ± 17	0.95 ± 0.18	5	188 ± 22	0.70 ± 0.08	6	84 ± 19	0.81 ± 0.16	5
Bulbectomized	217 ± 20	0.77 ± 0.10	8	194 ± 17	1.38 ± 0.39	6	71 ± 10	0.98 ± 0.12	5
BE+AM	99 ± 8*	0.67 ± 0.12	5	240 ± 15	0.73 ± 0.15	5	114 ± 9†	0.61 ± 0.05†	5
BE+TZ	144 ± 18†	0.66 ± 0.09	5	217 ± 12	0.60 ± 0.10	5	115 ± 17	0.65 ± 0.10	4
BE+IM	227 ± 17	0.64 ± 0.19	5	181 ± 7	0.48 ± 0.03	5	112 ± 11†	0.56 ± 0.08†	5

B_{max} (fmol/mg protein) and K_d (nM) values are means ± SEM calculated from n Scatchard plots. BE+AM, BE+TZ, and BE+IM represent the groups of bulbectomized mice treated with amitriptyline, trazodone, or imipramine, respectively.
*$p < 0.01$ and †$p < 0.05$ to bulbectomized group according to Student's two-tailed t-test.

TABLE 3

[^{3}H]SPIPERONE BINDING IN THE BRAIN REGIONS OF DBA/2j MICE: EFFECT OF BULBECTOMY AND ANTIDEPRESSANT TREATMENT

Group	Frontal cortex		Limbic area		Hypothalamus	
	B_{max}	K_d	B_{max}	K_d	B_{max}	K_d
Sham operated	581 ± 54	0.97 ± 0.13	1049 ± 21	1.05 ± 0.23	438 ± 20	0.65 ± 0.16
Bulbectomized	692 ± 33	1.08 ± 0.09	985 ± 38	0.71 ± 0.18	518 ± 43	0.65 ± 0.09
BE+AM	501 ± 83	2.85 ± 0.47*	907 ± 48	2.41 ± 0.23*	781 ± 100	1.79 ± 0.29*
BE+TZ	414 ± 11*	1.63 ± 0.13*	1023 ± 28	1.43 ± 0.12‡	489 ± 95	1.12 ± 0.18
BE+IM	518 ± 97	1.42 ± 0.11	762 ± 26*	1.41 ± 0.12‡	500 ± 41	0.81 ± 0.22

B_{max} and K_d values are means ± SEM calculated from five Scatchard plots. BE+AM, BE+TZ, and BE+IM represent groups of bulbectomized mice treated with amitriptyline, trazodone, and imipramine, respectively.

*$p < 0.01$ and ‡$p < 0.05$ to bulbectomized group according to Student's two-tailed t-test.

changes can appear in brain areas not connected directly with the olfactory bulbs.

The important question is whether the observed upregulation of these receptors caused by bulbectomy is connected with the intrinsic mechanisms of the behavioral syndrome found in bulbectomized mice and, in more broad context, with the neurochemical mechanisms of depression. In our previous study, we found that bulbectomized DBA mice, in contrast to C57 mice, did not display the behavioral syndrome typical for bulbectomized rats (35). Now, we detected no significant changes of 5-HT$_2$ receptor density in the FC in bulbectomized DBA mice. The results suggest that 5-HT$_2$ receptor upregulation in the FC in bulbectomized animals might be relevant to the bulbectomy-induced behavioral deficits.

Antidepressants always have been a powerful tool in studying animal models of depression. In the present study, the same doses of antidepressants and the same administration schedule were employed that we used in the study of the bulbectomy-induced behavioral disturbances in mice and the correction of them by antidepressant treatment (35). The comparison of the efficacy of the antidepressants in correcting the bulbectomy-induced behavioral deficits and in changing a particular receptor type can provide additional information that might help us understand better the connection between behavioral and receptor changes. Evidently, the three antidepressants tested did not affect 5-HT$_2$ receptors uniformly. In fact, only trazodone was able to counteract the effect of bulbectomy on this receptor type: It induced substantial downregulation of 5-HT$_2$ receptors in FC. At the same time, trazodone significantly decreased the density of these receptors in the LS, which was not altered by bulbectomy itself. The other two antidepressants did not alter significantly 5-HT$_2$ receptors in bulbectomized C57 mice. The different components of the bulbectomy-induced behavioral syndrome also had diverse sensitivity to the antidepressants (35). Trazodone was the most efficacious (imipramine came second, and amitriptyline had slight effect) in suppressing locomotor activity increased by bulbectomy in C57 mice. DBA mice, which did not show the 5-HT$_2$ receptor upregulation, displayed, however, elevated locomotor activity after bulbectomy corrected by the antidepressants. It does not necessarily mean that the upregulation of 5-HT$_2$ receptors caused by bulbectomy in C57 mice is not essential for the elevating of their locomotor activity because the organization of this behavior might be different in these two mice strains. Nevertheless, for several reasons it seems more likely that the upregulation of 5-HT$_2$ receptors in bulbectomized C57 mice is connected with the strong deficit in active avoidance learning they displayed (35). First, we found that bulbectomized DBA mice did not show active avoidance deficit (35), and at the same time we did not observe the increase of 5-HT$_2$ receptor density in FC. Second, trazodone much more effectively than the other antidepressants used restored active avoidance learning in C57 mice disrupted by bulbectomy (35), and it was the only one that decreased 5-HT$_2$ receptor density in the FC elevated in bulbectomized mice. Third, trazodone also significantly decreased 5-HT$_2$ receptor density in the FC (but not in the LS) in DBA mice: The effect was similar to that found in C57 mice. Correspondingly, trazodone was the only antidepressant that showed some positive effect on active avoidance learning in DBA mice, while the other two antidepressants impaired it.

Trazodone is a relatively new antidepressant with established clinical efficacy (4). Pharmacologically, trazodone differs from the other two antidepressants used because it does not affect norepinephrine (NE) or 5-HT reuptake mechanisms (4,13). Trazodone has been reported to have serotonin antagonistic activity (20) and high affinity to 5-HT$_2$ receptors as well (13). Trazodone in our study downregulated 5-HT$_2$ receptors, seemingly sharing this ability with the other 5-HT$_2$ antagonists (12,14,43). On the other hand, it failed to modify 5-HT$_2$ receptors in normal rats both after acute and chronic administration (17). We did not find the 5-HT$_2$ receptor downregulation in the brain regions studied after the treatment with amitriptyline or imipramine (except in case of imipramine in the LS in DBA mice), although it has been reported by others in the cerebral cortex (12,31,36,41) and hippocampus (31,36) in rats. The discrepancy may be due to the difference in the subjects: We studied bulbectomized mice, while in the other studies normal animals were used. Moreover, some antidepressant effects on the brain receptors have been found species (34,41) or even strain specific (46). It is also possible that these two antidepressants can induce 5-HT$_2$ receptor downregulation as a result of more prolonged treatment: 21–28 days (12,31, 36,41) instead of 14 days in the present experiments. Nevertheless, both amitriptyline and imipramine were able to decrease locomotor activity in both C57 and DBA bulbectomized mice (35) without decreasing the number of brain 5-HT$_2$ binding sites. They also more efficiently than trazodone restored passive avoidance in bulbectomized C57 mice. Therefore, it seems likely that some other receptor types are involved in these behavioral effects of the antidepressants.

Bulbectomy did not alter brain 5-HT$_{1A}$ receptors in C57

mice. It does not necessarily mean that these receptors are not related to the depression development and the mechanisms of antidepressant action. This receptor type was sensitive to chronic antidepressant treatment. Amitriptyline and trazodone induced the significant downregulation in the FC, while imipramine was ineffective. The antidepressants displayed the same pattern of efficacy in suppressing the elevated rearing in bulbectomized C57 mice (35). All antidepressants used (amitriptyline and imipramine significantly, and trazodone displaying the same tendency) increased 5-HT_{1A} receptor density and affinity in the HTH. The uniformity of the effects suggests that it might be important for their therapeutic activity. It has been shown that all three antidepressants restored passive avoidance learning in C57 mice with comparable efficacy (35). It seems likely, therefore, that this manifestation of antidepressant activity is associated with the increase of 5-HT_{1A} receptors in the HTH. The pharmacological and behavioral data so far indicated that the antidepressant actions were associated with downregulation of 5-HT_{1A} receptors (18,19,33). Chronic treatment with imipramine has been found to reduce 5-HT_{1A} receptors in the rat frontal cortex and hippocampus (30,31). On the other hand, autoradiographic study has shown the increase in the number of 5-HT_{1A} binding sites in the rat dorsal hippocampus, but not in the nucleus raphe dorsalis, after chronic amitriptyline treatment; the number of 5-HT_{1A} receptors in the whole-brain membranes was also increased (47). Thus, the data on the antidepressant effects on 5-HT_{1A} receptors are more controversial than on 5-HT_2 receptors and may depend upon the brain region examined, the species used, and the antidepressants used.

Bulbectomy appears to be a valid model of depression (22,39,48). This conclusion is based mostly upon the facts that bulbectomy brings about several physiological, hormonal, and biochemical changes resembling those found in depressive patients: increased blood corticosteroid level (22); disturbances in weight regulation (22); alterations in sleep regulation (15,40); decreased platelet serotonin uptake rate (8). Most of the bulbectomy-induced symptoms are alleviated by chronic, but not by acute, antidepressant treatment (5,6,22,23). The time course of the actions of antidepressants in bulbectomized animals is reasonably similar to the time course of their clinical actions in depressive patients. Bulbectomized animals display relatively high selectivity to the drugs with antidepressant activity in humans [for review, see (22,39,48)]. Moreover, the profound difference in the antidepressant action on the behavior between bulbectomized and sham-operated animals (22,23) resembles the difference in their action in normal people and depressive patients. All these facts allow us to hypothesize that bulbectomy might cause the neurological and neurochemical conditions similar to that in depressive patients. Bulbectomy appears to be an attractive model for studying the neurochemical basis of depression and antidepressant action also because it produces the steady pathology that allows to investigate the effects of chronic antidepressant treatment on the already-developed pathologic state. While working with some other animal models of depression based upon the effects of stress, such as learned helplessness or forced swimming, investigators usually employ chronic antidepressant pretreatment before depression-like syndrome actually develops.

It is generally believed that the serotonergic system is abnormal in depressive subjects. The exact nature of the abnormalities is far from clear. The present data support the hypothesis that depression is associated with 5-HT_2 receptor supersensitivity, probably resulting from serotonin deficiency. The data are in accord with the clinical observations that show 5-HT_2 receptor supersensitivity (2,49) in patients with major depressive disorders. Our results also support the notion that antidepressant-induced downregulation of central 5-HT_2 receptors might be involved in their therapeutic activity. The findings also show evidence that antidepressant treatment affects brain 5-HT_{1A} receptors and that these receptor alterations can be implicated in the behavioral activity of antidepressants. They are consistent with the earlier observations that central 5-HT_{1A} receptors might be involved in the mechanisms of antidepressant action (16,18,19,28,30,33,42).

We realize that direct comparison of the antidepressant effects on any particular form of behavioral deficit and on a particular type of receptor site is an oversimplification of the complex and intricate relationships. But, we believe that, despite the shortcomings, this is a promising approach to the elucidation of the neurochemical mechanisms underlying depression development and antidepressant action.

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