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Specific [^{3}H]8-OH-DPAT Binding in Brain Regions of Rats Genetically Predisposed to Various Defense Behavior Strategies

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POPOVA, N. K., D. F. AVGUSTINOVICH, V. G. KOLPAKOV AND I. Z. PLYUSNINA. *Specific [^{3}H]8-OH-DPAT binding in brain regions of rats genetically predisposed to various defense behavior strategies*. PHARMACOL BIOCHEM BEHAV **59**(4) 793–797, 1998.—Distribution of 5-HT$_{1A}$ receptors was studied in rats genetically predisposed to two basic defense strategies—passive (freezing) or active (aggression) defensive behavior. Specific [^{3}H]8-OH-DPAT binding was assayed in the brain structures of rat strains bred for 40 generations from Wistar stock for predisposition to freezing (catalepsy), and in wild rats bred for low and high aggression to humans. Considerable changes in [^{3}H]8-OH-DPAT binding were found in the brain of rats with hereditary predisposition to catalepsy. A significant decrease in B_{max} of specific receptor binding of [^{3}H]8-OH-DPAT in the frontal cortex, and in the striatum as well as an increase in K_d in the hippocampus of cataleptic rats was shown. A clear-cut tendency to decrease of 5-HT$_{1A}$ receptor density was observed in the midbrain and hypothalamus of these rats. A comparison of wild Norway rats bred for aggressiveness against humans with those bred for the absence of affective aggressiveness showed a B_{max} decrease without K_d change in the frontal cortex, hypothalamus, and amygdala of aggressive animals. It is hypothesized that 5-HT$_{1A}$ and probably 5-HT$_{1A}$-like 5-HT$_7$ serotonin receptors are involved in the mechanisms of both active and passive defense reactions, and the high expression of fear-induced defense is associated with their decrease in the frontal cortex. At the same time, the genetically determined preference for a certain defense behavior strategy depends either on the peculiarities of distribution of these receptor types in the brain regions or on some other types of serotonin receptors. © 1998 Elsevier Science Inc.

5-HT$_{1A}$ serotonergic receptors [^{3}H]8-OH-DPAT binding Rats Defensive behavior strategy Aggression to humans Hereditary catalepsy Genetic selection

THE fear-induced aggression and freezing (catalepsy) belong to basic kinds of defensive behavior. The defensive behavior strategy depends on both environmental (1) and genetic (14, 24) factors. Earlier, we obtained some data pointing to the participation of brain serotonin in the mechanisms of genetically defined freezing and of defensive aggression against humans. An elevated activity of the key enzyme of serotonin synthesis—tryptophan hydroxylase—was found in the striatum of freezing-prone rats, and its local elevation just in this structure was postulated to play the central role in the expression of genetic predisposition to catalepsy (13,21). Changes of different kinds have been found in the serotonergic system of rats bred for low aggression against humans. They have been detected in the midbrain where the bulk of serotonergic neuron perikarya are localized and the serotonin synthesis takes place. It has been demonstrated (22) that in the midbrain of wild rats bred for low aggression against humans, the tryptophan hydroxylase activity is increased, and in some brain structures so is the level of serotonin and of its main metabolite, 5-hydroxyindoleacetic acid. Similar changes in serotonin level and metabolism have been shown in the brain of silver foxes bred for low aggressiveness against humans (25). The homology of changes in the serotonergic system occurring during breeding for low aggressiveness in such remote species as foxes and rats has given reasons to hypothesize (22) that an increase in serotonin metabolism and in the functional activity

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of the brain serotonergic system is one of the factors causing the genetically determined attenuation of the fear-induced affective defense reaction. Accordingly, a high aggressiveness against humans seems to be associated with a decrease in brain serotonin synthesis and level.

The detected differences in serotonin metabolism in animals genetically predisposed to various types of defensive behavior raise the question as to the state of their serotonin receptor system. Of special interest is the A subtype of serotonin 5-HT_1 receptors. The group of 5-HT_1 receptors is a member of the G-protein receptor superfamily united on the basis of their relatively high structural homology, absence of introns in the genes, and presence of a common system of signal transduction (inhibition of adenylate cyclase), although they differ in their distribution in the brain, pharmacological profile, and physiological effects (8). The special attention for 5-HT_{1A} receptors is to a high degree associated with the data on their participation in the control of anxiety and depression (18). The balance between 5-HT_{1A} and 5-HT_{2A} serotonin receptors has been hypothesized to be also important for the therapeutic effect of antidepressants (2).

An important factor provoking anxiety and depression is fear. The fear is also a trigger of wild rat's aggression against humans, and of freezing. Earlier, we established the capacity of 5-HT_{1A} agonists to prevent the expression of catalepsy in rats hereditarily predisposed to this reaction (12). Agonists of 5-HT_{1A} receptors showed anticataleptic properties also in haloperidol-induced catalepsy (7). In this connection, a hypothesis arises that brain serotonin 5-HT_{1A} receptors participate in the control of catalepsy and that the considerable genotypic differences in susceptibility to catalepsy found by us (13) may be determined by hereditary differences in 5-HT_{1A} receptor density in brain structures. However, in the literature there are no data on peculiarities of serotonin receptors distribution in genetic predisposition to freezing reaction. At the same time, in autoradiographic assay (6) performed on wild rats in early generations of breeding for low aggressiveness, an increase of 5-HT_{1A} receptor density in limbic structures—gyrus dentatus and entorial cortex—and its decrease in the midbrain median raphe nucleus have been found.

A perspective model for studying hereditary peculiarities of brain transmitter systems in various kinds of defensive behavior is represented by rats bred during tens of generations for predisposition to catalepsy (11) and those bred for low or high aggression against humans (16).

The goal of the present radioligand study was estimation of specific [^{3}H]8-OH-DPAT binding in brain regions of rats with hereditary predisposition to catalepsy, or to high and low defensive aggression.

METHOD

Animals

Experiments were carried out on rats of a strain bred from outbred Wistar stock for high predisposition to catalepsy, and on wild Norway rats bred for absence of aggression, or, for contrarily, high aggression against humans. S40 males were used. The animals were kept under standard laboratory conditions with a free access to food and water, in groups of five individuals. Two days before the experiment, the animals were isolated into individual cages to remove the "group effect." Although cataleptic (freezing) reaction is characteristic of the strain bred for predisposition to catalepsy, it can not always be elicited in each given animal at the desired time. Therefore, for the experiments, animals with possibly most consistent predisposition to catalepsy were chosen. For this, rats of this strain were tested for catalepsy (11) five times before the experiment on different days, and experiments were made a week after the last testing only on those animals who consistently reacted with a pronounced catalepsy (maintenance of the imposed immobile vertical posture for no less than 10 s in no less than three tests out of five performed on different days).

Breeding for low aggressiveness against humans was started at the Institute of Cytology and Genetics in 1972 from wild Norway rats caught in the vicinities of Novosibirsk. Initially, selection involved rats with a comparatively low aggressive reaction, and in later generations, rats with no aggression against humans were selected, wherein inbreeding was avoided. Rats of S40 studied in our experiments were characterized by a complete absence of defensive reactions to handling, and by a negative "glove test," whereas the control rats reacted to a glove shown in front of the closed cage with frantic attacks. The animals were at an age of 3–5 months, weighed 300–350 g, and were kept under standard conditions with a free access to food and water, in groups of five individuals. Two days before the experiments, the rats were put into individual cages to remove the "group effect," and the effect of testing and were not disturbed any longer.

Radioligand Binding

Specific binding of [^{3}H]8-OH-DPAT to membranes from frontal cortex, midbrain, hypothalamus, amygdala, hippocampus, and striatum was assayed as described by Peroutka (19) with minor modifications (25). Brain tissues were homogenized in 40 vol of cold 50 mM Tris-HCl, pH 7.6. The homogenates were put into snow for 15 min to complete cell lysis and then spun at 20,000 $\times$ *g* for 25 min. The pellets were resuspended in the same volume of the buffer and spun at 20,000 $\times$ *g* for 25 min. The final pellets were resuspended in 20 vol of buffer. Binding assay mixture consisted of 0.9 ml suspension, 0.05 ml 0.125–4 nM [^{3}H]8-OH-DPAT (143.8 Ci/mmol, Du Pont, Germany), and 0.05 ml buffer or serotonin (10 μM, Reanal, Hungary) as the displaying drug. Following incubation at 37°C for 15 min samples were rapidly filtered through Whatman glass fiber GF/B filters that were washed with 3 $\times$ 5-ml cold buffer. The filters were then placed in glass vials containing 4 ml of a dioxane scintillator, and their radioactivity was measured on a Delta-300 scintillation counter. Specific binding was defined as the differences between the [^{3}H]8-OH-DPAT binding in the absence (total binding) and in the presence of (nonspecific binding) "cold" serotonin and expressed as fmol/mg protein.

Statistics

The B_{max} and K_d values for [^{3}H]8-OH-DPAT specific binding and their MSEs were calculated by the least-square method (4).

RESULTS

It has been found that the rats genetically predisposed to catalepsy showed some differences in 5-HT_{1A} receptor density distribution across brain regions compared with control Wistar rats (Table 1). A considerable decrease in B_{max} of [^{3}H]8-OH-DPAT binding in the frontal cortex and striatum, as well as a clear-cut tendency to decrease in the midbrain and hypothalamus were found. An especially great decrease of 5-HT_{1A} receptor density was observed in the frontal cortex

TABLE 1

THE DENSITY (B_{max}) AND AFFINITY (K_d) OF [^{3}H]8-OH-DPAT BINDING IN BRAIN AREAS OF WISTAR RATS AND RATS WITH GENETIC PREDISPOSITION TO CATALEPSY (GC)

	Wistar (n = 10)		GC (n = 10)	
Brain areas	B_{max} (fmol/mg of protein)	K_d (nM)	B_{max} (fmol/mg of protein)	K_d (nM)
Frontal cortex	101.1 ± 8.3	0.93 ± 0.13	41.9 ± 5.2†	0.76 ± 0.17
Hypothalamus	37.9 ± 4.8	0.74 ± 0.17	28.9 ± 5.1	0.63 ± 0.19
Hippocampus	224.1 ± 61.1	1.34 ± 0.54	158.1 ± 33.5	4.47 ± 1.13*
Striatum	16.2 ± 3.4	1.43 ± 0.39	7.5 ± 1.5*	0.83 ± 0.24
Midbrain	32.6 ± 3.9	1.25 ± 0.23	24.9 ± 4.3	1.01 ± 0.27

*$p < 0.05$, †$p < 0.001$ vs. Wistar.

where it was by more than two times lower than in the control rats. Some changes were found also in the hippocampus. Although 5-HT_{1A} receptor density in the hippocampus of cataleptic rats did not differ from that of control animals, the rats genetically predisposed to catalepsy were characterized by a lowered affinty of 5-HT_{1A} receptors: K_d in cataleptic rats was higher than in the control animals.

The study of specific [^{3}H]8-OH-DPAT binding in the brain of wild Norway rats showed that wild rats were characterized by a 5-HT_{1A} receptor distribution in the brain similar to that in the brain of laboratory rats and other mammalian species (10): the highest density of 5-HT_{1A} receptors was found in the hippocampus, high densities were also found in the amygdala and frontal cortex (Table 2). It is noteworthy that this distribution corresponds to the regional distribution of 5-HT_{1A} receptor RNA (15). At the same time, in rats with genetically low defensive reaction to humans, changes in the 5-HT_{1A} receptor density in some brain structure were found (Table 2). The clearest differences between aggressive and nonaggressive rats were found in the frontal cortex, hypothalamus, and amygdala where the 5-HT_{1A} receptor density in wild animals was considerably inferior to those of tame phenotype. B_{max} of specific receptor binding of [^{3}H]8-OH-DPAT in the hypothalamus of tame animals was by 63% ($p < 0.05$), in the frontal cortex by 57% ($p < 0.05$), and in the amygdala by 36% ($p < 0.05$) higher than in aggressive wild rats. At the same time, in the midbrain—the region of the main concentration of presynaptic somatodendritic 5-HT_{1A} receptors—no changes in specific [^{3}H]8-OH-DPAT binding were found. In neither of the brain regions studied were any changes in the K_d shown.

DISCUSSION

A multiannual selection of rats for predisposition to freezing reaction has resulted in creation of a unique strain (11). Earlier we established some considerable changes taking place in serotonin metabolism in the brain of genetically catalepsy-susceptible rats and demonstrated their similarity to changes occurring in catalepsy provoked by environmental factors (21).

The data given in the present study witness the occurrence of considerable changes in the serotonin receptor system in genetically catalepsy-susceptible rats. A clear-cut tendency to decrease of 5-HT_{1A} receptor density has been found in four out of five brain regions studied. The most pronounced changes of specific [^{3}H]8-OH-DPAT binding were found in the brain regions where postsynaptic 5-HT_{1A} receptors were mainly localized—in the frontal cortex, in the striatum, and in a limbic structure—hippocampus. However, an explicit tendency to decrease of the 5-HT_{1A} receptor density was noted also in the midbrain where, in the median and dorsal raphe nuclei, the bulk of presynaptic somatodendritic 5-HT_{1A} brain receptors was concentrated (29). Because stimulation of presynaptic receptors leads to a decrease of functional activity of the serotonergic system, and stimulation of postsynaptic receptors provokes specific serotonergic responses, involvement of the two kinds of 5-HT_{1A} receptors may integrally lead to rather complicated changes in serotonergic regulation.

It can be suggested that the decreased 5-HT_{1A} receptor density in the frontal cortex, striatum, and hippocampus is associated not only with the very predisposition to catalepsy, but also with some other behavioral properties of rats predisposed to this freezing reaction, for example, such as the ear-

TABLE 2

THE DENSITY (B_{max}) AND AFFINITY (K_d) OF [^{3}H]8-OH-DPAT BINDING IN BRAIN AREAS OF AGGRESSIVE AND TAME NORWAY RATS

	Tame (n = 10)		Aggressive (n = 10)	
Brain areas	B_{max} (fmol/mg of protein)	K_d (nM)	B_{max} (fmol/mg of protein)	K_d (nM)
Frontal cortex	145.1 ± 17.8	1.06 ± 0.34	92.2 ± 8.0*	1.13 ± 0.27
Hypothalamus	64.8 ± 9.0	0.77 ± 0.18	39.7 ± 4.9*	0.60 ± 0.10
Hippocampus	218.7 ± 31.9	1.16 ± 0.27	222.2 ± 30.7	1.61 ± 0.32
Amygdala	211.2 ± 20.9	0.56 ± 0.10	54.2 ± 14.5*	0.66 ± 0.11
Midbrain	25.8 ± 10.0	1.78 ± 0.97	26.5 ± 9.2	1.28 ± 0.68

*$p < 0.05$ vs. tame rats.

lier shown (17) enhancement of emotional reaction to humans, and longer immobility time in Porsolt's test. This suggestion is based on the data demonstrating that 5-HT_{1A} agonists possess an anxiolytic effect (3,26) and prevent catalepsy (12). The 5-HT_{1A} deficit found in the midbrain of cataleptic rats probably contributes to expression of catalepsy, because it has been shown that 5-HT_{1A} activation in the midbrain median raphe nucleus (a structure with the highest density of presynaptic 5-HT_{1A} receptors) decreases serotonin release in the striatum (9), i.e., in the structure whose serotonergic function is associated with development of catalepsy (20).

Changes in 5-HT_{1A} receptors have been also found in another kind of genetically defined defensive behavior—fear-induced aggression against man. This was demonstrated by comparing wild rats bred for high and low aggression. The most clear-cut differences between aggressive and nonaggressive rats were observed in the frontal cortex, in the hypothalamus, and the amygdala—brain regions with preferentially postsynaptic localization of 5-HT_{1A} receptors. Involvement of the hypothalamus in the control of aggressive behavior is beyond any doubt, and has been confirmed by numerous data (23). The increased density of serotonin 5-HT_{1A} receptors in the hypothalamus of nonaggressive rats may account for the altered hormonal regulation found in rats bred for low aggression, i.e., a decrease of functional activity of the hypothalamus–pituitary–adrenal system (16) and hypothalamus–pituitary–testicular complex (30). Lately, evidence has been accumulated for involvement of serotonin 5-HT_{1A} receptors of amygdaloid complex in the control of the emotional state, although the data on their influence are contradictory. On the one hand, a bilateral injection of 5-HT_{1A} agonists ipsapirone, buspirone, and 8-OH-DPAT into the amygdala decreased the electric current-induced ultrasonic vocalization, which is regarded as an index of anxiety attenuation (28). On the other hand, experimental data demonstrate that the amygdala serotonin enhances anxiety and fear (5). The increase in the density of 5-HT_{1A} receptors in the limbic structures of low-aggressive rats found by us are to some extent in accordance with the results obtained when studying the distribution of this receptor type by the autoradiographic method (6). In these studies carried out on nonaggressive wild rats of the first breeding generations an increase of [^{3}H]8-OH-DPAT label was found in some brain structures, the maximal increase being observed in the limbic system.

It is noteworthy that although 8-OH-DPAT is considered as the most selective 5-HT_{1A} agonist, recently its rather high affinity to 5-HT_7 serotonin receptors was found (15), which gives reasons to regard them as 5-HT_{1A}–like receptors positively coupled with adenylate cyclase (27). The 5-HT_7 receptor type has not been studied much, and its physiological profile is so far obscure. However, its high affinity to 8-OH-DPAT makes one interprete more cautiously the [^{3}H]8-OH-DPAT binding peculiarities found in aggressive and in cataleptic rats attributing them not exclusively to 5-HT_{1A} receptor type but rather to 5-HT_{1A}/5-HT_{1A}–like receptors. In this way, both in rats genetically predisposed to passive defense (freezing reaction) and in rats with a manifest active defense (aggression), changes in 5-HT_{1A}/5-HT_{1A}–like brain receptors have been found. The greatest coincidence of changes was shown in the frontal cortex where the B_{max} of [^{3}H]8-OH-DPAT binding in rats predisposed to freezing reaction and in highly aggressive ones was decreased by 58 and 37% against respective controls (animals who did not exhibit the mentioned types of defensive behavior).

A considerably decreased 5-HT_{1A}/5-HT_{1A}–like receptor density in highly aggressive rats compared to low aggressive ones, and a clear-cut tendency to its decrease in cataleptic rats were found in hypothalamus. Differences between animals genetically predisposed to different types of defensive behavior were found in hippocampus where a considerable increase in K_d was found in rats predisposed to freezing reaction vs. Wistar controls, indicating a diminished receptor affinity to the ligand, while no differences were shown between rats with high and low aggressive defense reactions. Neither were any changes observed in the midbrain of aggressive vs. nonaggressive rats, although there was a clear-cut tendency to decreased B_{max} in cataleptics vs. Wistar.

It is noteworthy that these changes have the same direction: in the two types of hereditarily determined defensive behavior a decreased density of receptors for specific [^{3}H]8-OH-DPAT binding was found in some brain structures. Because the main factor inducing both kinds of defensive reaction is fear, one may hypothesize that the genetically determined predisposition to defensive behavior is mediated via involvement of 5-HT_{1A}/5-HT_{1A}–like receptors, and the anxiety and fear that trigger various kinds of defensive behavior are associated with a reduced density of these receptors.

The genetically defined preference of some or other strategy of defense seems to be determined by the peculiarities of serotonin metabolism in some brain regions, i.e., an increased serotonin metabolisn in the striatum predisposes animals to freezing (20,21) and highly expressed fear-induced aggression is associated with a decreased serotonin metabolism in midbrain and some other brain regions (22,25). As to serotonergic receptors, it can be supposed that in the genetically defined predisposition to active or passive strategy of defense either regional distribution of 5-HT_{1A}/5-HT_{1A}–like serotonin receptors or, possibly, some other types of brain serotonergic receptors play a role.

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