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Review

Stress- and antidepressant treatment-induced modifications of 5-HT$_7$ receptor functions in the rat brain

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Abstract:
This paper summarizes a series of electrophysiological studies aimed at finding the effects of the activation of 5-HT$_7$ receptors on neuronal excitability as well as on excitatory and inhibitory synaptic transmission in the hippocampus and in the frontal cortex of the rat. These studies demonstrated that 5-HT$_7$ receptors play an important role in the modulation of the activity of the hippocampal network by regulating the excitability of pyramidal cells of the CA1 area, as well as *via* their effect on GABA and glutamatergic transmission. The reactivity of 5-HT$_7$ receptors in the hippocampus is decreased by repeated administration of antidepressant drugs and increased by a prolonged high level of corticosterone. More importantly, administration of antidepressant drug, imipramine, prevents the occurrence of corticosterone-induced changes in the function of hippocampal 5-HT$_7$ receptors. It has also been found that the blockade of 5-HT$_7$ receptors by the selective antagonist SB 269970, lasting for a few days, causes similar changes to those observed after long-term administration of antidepressants. Thus, it seems that the pharmacological blockade of 5-HT$_7$ receptors produces faster effects compared to classic antidepressant drugs. A similarity between the changes in the glutamatergic transmission induced by the blockade of 5 HT$_7$ receptors and those caused by repeated administration of the antidepressant drug, imipramine, has also been found in the frontal cortex. It has also been shown that the changes in glutamatergic transmission and the impairment of long-term synaptic plasticity in the frontal cortex of animals subjected to repeated restraint stress are reversed by the blockade of 5-HT$_7$ receptors.
Overall, these studies, together with the data provided by other investigators, support the hypothesis that 5-HT$_7$ receptor antagonists may become a prototype of a new class of antidepressant drugs. Such compounds will not function by blocking 5-HT reuptake, as many of the currently used drugs, but through a direct interaction with the 5-HT$_7$ receptor. This type of action is highly selective and usually does not require the occurrence of adaptive changes in neuronal functions, thus allowing for a much quicker therapeutic effect.

Key words:
antidepressants, brain slices, frontal cortex, hippocampus, model of stress, serotonin receptors

Abbreviations: 5-HT – 5-hydroxytryptamine, serotonin, CNS – central nervous system, DRN – dorsal raphe nuclei, I(h) – hyperpolarization-activated current, sAHP – slow afterhyperpolarizing potential, SCN – suprachiasmatic nucleus, SSRI – selective serotonin reuptake inhibitor(s)

Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is involved in a variety of physiological and cognitive processes in-

cluding sleep, sensory perception, motor activity, temperature regulation, appetite, hormone secretion, nociception and sexual behavior [40]. In the central nervous system (CNS), serotonin activates numerous 5-HT receptors which have been classified as belonging to seven families and 15 subtypes, on the basis of their pharmacological properties, coupling to intracellular signaling cascades and protein structure [38]. With the exception of the 5-HT_3 receptor, being a ligand-gated ion channel, the remaining ones belong to the class of G-protein coupled metabotropic receptors. However, their diversity, interactions with other neurotransmitter systems and the fact that some 5-HT receptors subtypes do not yet have a complete functional, biochemical and physiological characteristics, make it difficult to obtain a full description of the functions and roles played by 5-HT in the CNS.

Although the last of the serotonin receptor subtypes, the 5-HT_7 receptor, was identified already almost two decades ago [6, 81, 82], the knowledge of the effects of its activation and functions in the CNS is not yet fully developed. The 5-HT_7 receptor has been implicated in mood regulation, circadian rhythmicity and sleep, the disturbances of which are evident in the course of depressive disorders [36, 88]. Moreover, some antidepressants exhibit a high affinity for this receptor [1, 52]. Since there are reasons to believe that it may be involved in the etiology of mental illnesses, this receptor is presently considered one of the most attractive research targets in this regard [34, 60, 61].

Early research of the functions of 5-HT_7 receptors concentrated on neurons of the hypothalamic suprachiasmatic nuclei (SCN), comprising the "biological clock" in the mammalian brain. *In vitro* [37, 53, 85, 104, 105] as well as *in vivo* [4, 22] animal studies, conducted using nonselective 5-HT_7 receptor agonists, demonstrated that their effects such as phase shifting of circadian rhythms, inhibition of spontaneous activity and inhibition of the light stimulation, were diminished by the selective 5-HT_7 receptor antagonists SB 269970 and DR 4004. Moreover, down-regulation of the 5-HT_7 receptor has been found to occur in rat SCN after chronic treatment with tricyclic antidepressants and the SSRI fluoxetine [63, 84]. The implication of the 5-HT_7 receptor in circadian rhythm phase resetting and the involvement of 5-HT_7 receptor-selective antagonists in altering rapid eye movement (REM) sleep parameters in an opposite pattern to that observed in human patients with clinical depression, was confirmed in the study conducted on 5-HT_7 receptor knockout mice [35, 60, 89].

Antidepressant drugs currently used in psychiatry are effective only in part of patients and do not always produce a complete cure. A successful therapy requires prolonged administration of the drug, which often causes a number of onerous (and sometimes hazardous to health) side-effects [46]. Therefore, an extensive search for new, more effective and safe antidepressant drugs is still to be carried out. Two research groups have shown an antidepressant-like action of the 5-HT_7 receptor antagonist SB 269970 in animal models of depression: the forced swim and tail suspension tests [35, 101]. Interestingly, the data suggest that the 5-HT_7 receptor antagonist, SB 269970, raises the level of 5-HT in brain structures thought to be involved in the pathophysiology of depression i.e., hippocampus, frontal cortex and dorsal raphe nuclei (DRN) [101], but the mechanism of this effect is unclear, since 5-HT_7 receptors are expressed both in the DRN as well as in brain structures which receive the serotonergic innervation [33, 56, 80]. Generally, the available data indicate that activation of 5-HT_7 receptors leads to an increase in the excitability of neurons on which they are localized. For example, experiments conducted on the anterodorsal thalamic neurons have demonstrated that 5-HT_7 receptors mediate membrane depolarization *via* an increase of the hyperpolarization-activated current I(h) [16, 17]. Similarly, the 5-HT_7 receptor-dependent modulation of I(h) is also one of suggested mechanism of the increase of the excitability in rat dorsal root ganglion neurons [14]. The stimulatory effect of the activation of 5-HT_7 receptors on synaptic transmission has also been shown in deep dorsal horn neurons [27]. It has been speculated that 5-HT_7 receptor antagonist-induced increase in brain serotonin release is due to a complex GABA-glutamatergic-serotonergic interaction in the DRN [33, 43, 80] and it has been suggested that 5-HT release may be mediated *via* blockade of 5-HT_7 receptors localized on GABAergic interneurons in the DRN [21]. The studies conducted by Roberts et al. [80] and Glass et al. [29] have suggested that 5-HT_7 receptors in the DRN are localized, among others, on GABAergic cells. However, mainly due to the lack of selective agonists, there are no detailed characteristics of the effects of activation and blockade of the 5-HT_7 receptor in those brain structures, which are thought to be most important in the context of pathophysiology of affective disorders.

The effects of 5-HT$_7$ receptor activation on hippocampal excitatory and inhibitory neurons and synaptic connections

In order to get insight into the role played in normal conditions by the 5-HT$_7$ receptor in excitatory and inhibitory neurons of the hippocampus, a brain structure receiving a massive serotonergic innervation, the effects of the activation of this receptor were investigated in the CA1 area using whole-cell recording in rat *in vitro* brain slices. Due to a lack of a selective 5-HT$_7$ receptor agonist, in order to activate 5-HT$_7$ receptors a wider-spectrum serotonin agonist 5-CT was applied in the presence of WAY 100635, a selective 5-HT$_{1A}$ receptor antagonist, the latter being introduced into the slice incubation medium at least 1 h before 5-CT. The results indicate that the 5-HT$_7$ receptor increases the excitability of excitatory, pyramidal neurons *via* a reduction in the amplitude of the slow afterhyperpolarizing potential (sAHP), an attenuation of the spike frequency adaptation and 2 to 6 mV depolarization [97]. The mechanism of the 5-HT$_7$ receptor-mediated decrease of sAHP and the reduction of the spike frequency adaptation has been attributed to the inhibition of Ca^{2+}-activated K^+ channels (K_{AHP}). Earlier research from this laboratory demonstrated that these channels play an important role in modulation of excitability of CA1 pyramidal neurons [9]. It has been shown that numerous types of excitatory receptors (a.o., 5-HT$_4$, β-adrenergic, muscarinic, histaminic, metabotropic glutamate mGluR1) close potassium channels of this type. It appears that these channels are deactivated *via* phosphorylation, mainly by the protein kinase A (PKA), but also by the protein kinase C (PKC) [9]. The findings reported by other researchers confirm that 5-HT$_7$ receptors modulate the excitability of hippocampal pyramidal neurons of the CA3 area by closing potassium channels of the K_{AHP} type [5].

The activity of hippocampal excitatory, pyramidal neurons remains under control of GABAergic feed-forward or feed-back connections [24, 25]. It has been suggested that the activation of 5-HT$_7$ receptors modulates the function of GABAergic interneurons in the raphe nuclei [80]. The activation of 5-HT$_7$ receptors enhances the excitability of GABAergic neurons in globus pallidus [18] but 5-HT$_7$ receptors decrease GABA-dependent currents in the SCN [43]. Therefore, we examined the effect of the activation of 5-HT$_7$ receptors on GABAergic, spontaneous postsynaptic inhibitory currents (sIPSCs) recorded from CA1 pyramidal neurons.

The activation of 5-HT$_7$ receptors increased the mean sIPSCs frequency while the mean sIPSCs amplitude remained unchanged [93]. An increased frequency of spontaneous postsynaptic currents reflects either the enhanced firing of presynaptic cells, or increased neurotransmitter release and/or changes in the number of neurotransmitter release sites. Hence, several mechanisms may potentially account for the observed 5-HT$_7$ receptor-dependent enhancement of GABA release. It is conceivable that 5-HT$_7$ receptor activation directly raises the excitability of interneurons and/or increases the release of GABA *via* activation of 5-HT$_7$ receptors located on presynaptic terminals. Alternatively, the enhanced release of GABA may be an indirect consequence of the increased glutamatergic, excitatory input to GABAergic cells due to activation of 5-HT$_7$ receptors located in the perisomatic region of glutamatergic neurons. Immunohistochemical studies have demonstrated the presence of 5-HT$_7$ receptors on the cell bodies of pyramidal neurons in the CA1 area [8]. Indeed, successive experiments indicated an increase in the frequency of sEPSCs recorded from interneurons after 5-CT application [93]. Furthermore, after the blockade of glutamatergic transmission by the nonselective antagonist, kynurenic acid [26, 74], the magnitude of 5-HT$_7$ receptor-induced effect on the frequency of sIPSCs recorded from pyramidal cells was significantly weaker [93]. Hence, the above data suggest that 5-HT$_7$ receptor-induced increase in GABA release is partly due to the increased excitatory input to GABAergic neurons.

Another mechanism underlying the stimulatory effect of 5-HT$_7$ receptor activation on sIPSCs frequency seems to operate through 5-HT$_7$ receptors localized on GABAergic cells. To the best of our knowledge, there are no data which would confirm the expression of these receptors in hippocampal interneurons. However, several authors have concluded that 5-HT$_7$ receptors are expressed, for example, in GABAergic cells in the DRN [20, 21, 29, 80]. The increase in interneuron firing rate cannot account for the observed effect on sIPSCs frequency, as no 5-CT-induced changes in GABAergic interneuron excitability have been reported [93]. Moreover, in the presence of kynurenic acid and, additionally, TTX, the sodium channel blocker, activation of 5-HT$_7$ receptors still in-

duced an increase in sIPSCs frequency [93]. Thus, it seems conceivable that 5-HT_7 receptors modulate the release of GABA from axon terminals. Further studies using immunochemical methods are necessary to verify the expression of 5-HT_7 receptors on hippocampal GABAergic interneurons.

The influence of corticosterone and antidepressant drugs on the reactivity of the 5-HT_7 receptor in hippocampal neurons

Our earlier experiments have shown that electroconvulsive therapy (ECS) and repeated administration of antidepressants (imipramine, citalopram) increase the inhibitory effect of 5-HT in the hippocampus *via* two mechanisms: (a) the increased response to the activation of inhibitory 5-HT_{1A} receptors and (b) the diminished effect of activation of excitatory 5-HT_4 receptors [10, 90]. To study the influence of antidepressant drugs on the effect of activation of 5-HT_7 receptors, our laboratory used the measurements of spontaneous epileptiform bursts, recorded from the CA3 hippocampal area under nominally Mg^{2+}-free incubation conditions in rat *in vitro* brain slices. Activation of 5-HT_7 receptors induced an increase in the frequency of spontaneous epileptiform bursts, recorded from the CA3 area under nominally Mg^{2+}-free incubation conditions, was increased after 5-CT application [96]. In this experimental model, repeated treatment with the SSRI, citalopram, or the tricyclic antidepressant, imipramine, resulted in attenuation of the excitatory effects of activation of hippocampal 5-HT_7 receptors [96].

The repeated stressors often cause a variety of disturbances and irregularities in the cognitive, emotional and physiological processes of the organism [58, 107]. A chronic high level of corticosteroid hormones (cortisol in humans and corticosterone in rodents) leads to hyperactivity [77], deregulation of the functions of the hypothalamus-pituitary-adrenal (HPA) axis and disrupts the mechanism of the HPA axis negative feedback [64, 87]. Since a prolonged elevation of plasma cortisol level often occurs in the course of depressive disorders in human patients, it has been commonly accepted that long-lasting alterations in the activity of the HPA axis are a risk factor to the precipitation of the disease [71]. Repeated corticosterone administration has often been used as an animal model for studying the effects of prolonged stress and a role of stress in depression [86, 100, 109]. It has been shown that corticosterone injections repeated for 21 days increased the percentage of immobility time and decreased the percentage of swimming time in a forced swim test; those two effects being commonly regarded as a depression-like behavior in rats [31]. A specific advantage of this model is the elimination of the adaptation of the organism to a repeated stressor [64, 65, 77]. An earlier study from this laboratory showed that repeated corticosterone administration caused changes in the reactivity of 5-HT_{1A} and 5-HT_4 receptors in the CA1 area of the hippocampus, which were reversed by a simultaneous treatment with imipramine [108]. Testing the effects of the activation of 5-HT_7 receptors has proven that repeated corticosterone administration increased the reactivity of rat CA3 hippocampal circuitry to the activation of this receptor. Moreover, it has been demonstrated that imipramine, administered concurrently with corticosterone, counteracted changes occurring due to corticosterone. It has also been shown that in rats treated with corticosterone and imipramine, the functional modification in the reactivity of 5-HT_7 receptors was not accompanied with changes in the binding of the selective ligand [^{3}H]SB 269970 [95]. These results suggest that imipramine and corticosterone treatments modify neither the number of receptors nor their binding properties but they influence in an opposite manner the signaling cascades downstream the receptor. These modifications are likely to involve changes in the capacity of the receptor to activate G protein and/or changes in G protein expression or phosphorylation [15, 50, 69]. These data are consistent with the results obtained by other investigators who demonstrated that multiple ECS, lithium and fluoxetine reduced the quantity of mRNA for the α subunit of the Gs protein in the CA1 hippcampal area [48, 59], while fluoxetine, imipramine, clomipramine, desimipramine and clorgyline also reduced the protein amount of the α subunit of the Gs [50, 49].

The influence of the blockade of the hippocampal 5-HT_7 receptor on its reactivity

Recent research has demonstrated a synergistic interaction between compounds acting as 5-HT receptor antagonists and several antidepressant drugs, including the specific 5-HT_7 receptor antagonist SB 269970.

Moreover, inactivation and blockade of the 5-HT$_7$ receptor have been shown to induce antidepressant-like behavioral effects in animal models [32, 35, 101, 102]. Several psychotropic drugs exhibit a high affinity for 5-HT$_7$ receptors [52]. Our earlier study indicated an attenuation of the effects of the activation of 5-HT$_7$ receptors in rat hippocampus after treatment with the antidepressant drugs, imipramine and citalopram [96]. Collectively, these findings support the hypothesis that one important mechanism of the therapeutic effects of chronic treatment with antidepressants may be related to the blockade of the 5-HT$_7$ receptor.

Since only acute administration of the 5-HT$_7$ receptor antagonist SB 269970 has been investigated before, we set up to examine and compare the effects of acute and prolonged treatment with SB 269970 on the reactivity of the 5-HT$_7$ receptor using a biochemical and electrophysiological approach. The obtained results showed that both acute and repeated treatment with SB 269970 decreased the reactivity of the 5-HT$_7$ receptor assessed with the use of the recording of spontaneous epileptiform activity in the hippocampal CA3 area under nominally Mg^{2+}-free incubation conditions [98]. The mechanisms underlying the observed attenuation of the excitatory effect of the 5-HT$_7$ receptor activation by SB 269970 may potentially be related to either the decreased receptor density or the modification in the capacity of the receptor to activate G protein, changes in G protein expression or phosphorylation, or modifications at the level of effectors. The data demonstrated that both single and repeated SB 269970 administration lowered the level of mRNA of those G proteins (G*a*s and G*a*12) which couple to the 5-HT$_7$ receptor in the hippocampus [103]. Repeated treatment with SB 269970 also decreased the density of 5-HT$_7$ receptors [98]. These effects differed markedly from the effects of the antidepressant imipramine, which altered neither the level of the mRNAs nor the density of 5-HT$_7$ receptors when administered once or repeatedly for 14 days. Also, in contrast to imipramine, repeated SB 269970 administration decreased the mean basal bursting frequency in hippocampal slices. The most likely explanation of this phenomenon is a reduction of excitatory synaptic transmission due to SB 269970 treatment. These results indicate that changes induced by the administration of SB 269970 depend, at least in part, on the mechanisms which are different from those underlying the effects of the antidepressant drug imipramine.

Besides modulation of membrane excitability, activation of hippocampal 5-HT$_7$ receptors has been shown to stimulate neurite outgrowth [47]. Both G*a*s and G*a*12 proteins can regulate cellular morphology by activating different signaling cascades. G*a*s protein-mediated morphogenic effects are produced by either modulation of cAMP concentration [19] or a direct binding of the G*a*s protein to the cytoskeleton [106]. Downstream G*a*12 protein effectors, which mediate changes in the actin cytoskeleton, are members of the Rho family of small GTPases, including RhoA, Rac1 and Cdc42 [41]. The major functional effects of this pathway include actin reorganization and the formation of neurite-like protrusions and are mediated by the activation of Cdc42 [47]. It is proposed that the activation of the 5-HT$_7$ receptor by G*a*s and G*a*12 proteins may stimulate glutamatergic synaptic transmission by a positive influence on a number of functional synapses. Hence, the prolonged blockade of the 5-HT$_7$ receptor, resulting in a decreased expression of G*a*s and G*a*12 proteins, might account for the observed reduction of glutamatergic transmission.

Thus, the experiments showed that the blockade of the 5-HT$_7$ receptor by SB 269970 led to a functional desensitization of the 5-HT$_7$ receptor system at the level of effector proteins, although we note that changes in the receptor density occurred after chronic treatment with the antagonist. The phenomenon of 5-HT$_7$ receptor system downregulation may be an important factor in the mechanism of the antidepressant effect of the 5-HT$_7$ antagonist, as well as in the modulation of reactivity of other neurotransmitter systems.

The influence of antidepressant drugs and the blockade of 5-HT$_7$ receptors on glutamatergic transmission in rat frontal cortex

Emotional and cognitive processes, which are disrupted in course of affective disorders, depend on the limbic areas of the brain. The limbic system is connected with the frontal cortex, a part of the cerebral cortex responsible for the integration of emotional reactions with cognitive processes and the control of behavior. The abnormalities in cognitive functions and emotional behavior occurring during depressive disorders implicate the involvement of the frontal cortex in the pathophysiology of depression and in the action of antidepressant drugs [44, 45, 55].

A growing body of evidence indicates that abnormalities in the glutamatergic transmission play an important role in the pathophysiology of mood disorders, and that the common mechanism of antidepressant therapies involves modifications in the function of the glutamatergic system [46, 70, 72]. The unmet need for an improved pharmacotherapy of treatment-resistant depression has resulted in a search for new compounds with new mechanisms of action such as those expressing affinity for glutamate receptors [7, 42, 54, 70]. It has been shown that N-methyl-D-aspartate (NMDA) receptor antagonists exhibit antidepressant-like actions in animal behavioral models and potentiate the effects of antidepressants [99]. It has also been established that chronic treatment with various antidepressants results in a reduction of the radioligand binding to rat cortical NMDA receptors [66, 67]. On the basis of these findings it has been hypothesized that the mechanism of antidepressant action is related to the attenuated function of NMDA receptors in the cerebral cortex [75, 83]. According to the glutamate hypothesis of depression, the glutamatergic system is a primary mediator of psychiatric pathology and, potentially, also a final common pathway for the therapeutic action of antidepressants [3, 39, 46].

Despite a substantial body of evidence indicating the involvement of adaptive changes in the function of NMDA receptors during antidepressant therapies, no attempts have yet been made to assess changes in cortical glutamatergic receptor functions using an electrophysiological approach. Therefore, we aimed at finding effects of repeated administration of the tricyclic antidepressant, imipramine, on glutamatergic transmission in rat frontal cortex using whole-cell recording. Since our previous study showed that serotonin, acting *via* 5-HT_7 receptors, exerted significant modulatory influence on synaptic transmission in rat hippocampus, it was conceivable that the antidepressant-like effects of the 5-HT_7 receptor antagonist may be related to its modulatory action on glutamatergic transmission also in the cortex. Therefore, we also investigated the effects of single and repeated administration of the 5-HT_7 antagonist SB 269970 on glutamatergic neurons and excitatory synaptic transmission in slices of the rat cortex. Our study showed that repeated administration of imipramine and SB 269970 strongly reduced the mean frequency and, to a smaller extent, the mean amplitude of sEPSCs recorded from layer II/III cortical pyramidal neurons 2 days after termination of the treatment [94, 92].

Frontal cortex receives a dense serotonergic input from the DRN [68]. Being released from axon terminals of the raphe neurons, serotonin has been shown to affect the action of several neurotransmitters by the heterosynaptic activation of 5-HT receptors located on neighboring axon terminals [23]. The heterosynaptic activation of 5-HT receptors on glutamatergic neurons has been shown to inhibit or stimulate glutamate release in the cortex *via* 5-HT_{1A}, 5-HT_{1B} or 5-HT_{2A} receptors, respectively [13, 30, 57]. Hence it is conceivable that the decrease in glutamatergic transmission after repeated imipramine or chronic blockade of 5-HT_7 receptors, observed in our study, occurs as a result of the activation of other classes of 5-HT receptors, but not 5-HT_7 receptors, by a prolonged elevation of the 5-HT level in the cortex induced by the blockade of 5-HT_7 receptors in the DRN. So far, only a few studies have examined the effect of SB-269970, administered alone or jointly with antidepressant drugs, on 5-HT release in the cortex. Wesołowska and Kowalska [101] demonstrated that both SB-269970 and imipramine increased the efflux of DA, NA and 5-HT in rat prefrontal cortex. On the other hand, some authors found that SB-269970 significantly inhibited 5-HT efflux [79].

It is well known that the functional changes that occur within the presynaptic terminals affect the frequency of sEPSCs, while the amplitude of postsynaptic currents depends on both presynaptic factors, such as the amount of neurotransmitters in synaptic vesicles, and postsynaptic ones – mainly the number of receptors for the neurotransmitter e.g., [78]. It is conceivable that the observed decrease in the frequency of sEPSCs may potentially result from the imipramine- or SB 269970-induced decrease in the spontaneous firing of cells synapsing on neurons from which the recording was made. However, all recorded cells showed no spontaneous spiking during the initial current-clamp recording at the resting membrane potential. Moreover, the lack of a significant change in the mean frequency of sEPSC after the blockade of Na channels in the tested sample of neurons suggested that a majority of recorded sEPSCs corresponded to miniature EPSCs whose frequency is not related to the spiking activity of presynaptic cell. Hence, an approximately two-fold decrease in the sEPSC mean frequency, observed in the present study, resulted from the diminution of glutamate release [51].

The observed reduction in the mean amplitude of sEPSCs may principally result from changes in the membrane resistance, however, neither imipramine

nor SB 269970 affected the basic electrophysiological parameters of the recorded neurons (input resistance, resting membrane potential and excitability). The comparison between the NMDA and the AMPA/kainate receptor-mediated electrically evoked EPSCs ratio indicated that, at least in the case of imipramine, chronic treatment led to a relative reduction of the NMDA receptor-mediated response and/or decrease in its density [92].

The effects of repeated stress and the 5-HT$_7$ receptor antagonist on long-term potentiation in rat frontal cortex

Memory disturbances belong to the most common symptoms of depression and other illnesses caused by repeated stress or traumatic experiences. For example, repeated restraint stress has been shown to induce a strong desensitization of the hypothalamic-pituitary-adrenal axis and an elevation of plasma corticosterone level e.g., [28]. Long-term potentiation (LTP) of synaptic transmission is an experimental model of cellular and molecular changes that seem to underlie the formation and maintenance of memory traces in the brain**.** The processes involved in the induction and maintenance of LTP are still not fully understood, but an external manifestation of this phenomenon, i.e., the activity-dependent increase in the efficiency of synaptic connections lasting for several weeks, is an example of the strengthening of synaptic connection, depending on simultaneous pre-and postsynaptic activity. LTP has been shown to be suppressed by repeated stress [2, 73]. It has been well documented that, in general, chronic stress disrupts neural plasticity, while antidepressant drugs produce an opposite effect [76].

We investigated the effect of repeated restraint stress on glutamatergic field potentials and LTP in rat frontal cortex. The animals were subjected to restraint lasting 10 min twice daily for 3 days. The 5-HT$_7$ receptor antagonist SB 269970 was administered before each restraint stress session and would prevent the occurrence of changes induced by repeated exposure to stress. The obtained data indicate that the 5-HT$_7$ receptor antagonist SB 269970 prevents the occurrence of the restraint stress-induced enhancement of glutamatergic transmission and attenuation of LTP in rat frontal cortex [91]. We also demonstrated that repeated corticosterone treatment enhances excitatory synaptic transmission and impairs LTP in rat frontal cortex, whereas the tricyclic antidepressant imipramine, administered jointly with corticosterone, normalizes the enhanced basal excitatory synaptic transmission and the reduced potential for long-term synaptic plasticity, evoked by repeated corticosterone administration [11]. Intraperitoneal administration of SB-269970 raises the extracellular levels of serotonin as well as these of dopamine, noradrenaline in rat prefrontal cortex, thus resembling the effect of administration of antidepressant drugs [12, 33, 101]. It may be hypothesized that the elevated level of 5-HT and/or noradrenaline compensates the effect of restraint stress on glutamatergic transmission and synaptic plasticity.

Conclusions

The data obtained in the course of studies summarized here indicate that serotonin, by acting through 5-HT$_7$ receptors, exerts modulatory influence on hippocampal excitatory cells and on glutamate and GABA mediated synaptic transmission in rat hippocampus. Since the prolonged blockade of 5-HT$_7$ receptors decreases glutamatergic transmission in the frontal cortex in a similar way as does imipramine, and it restores the capacity of cortical excitatory synapses to undergo antagonists of the 5-HT$_7$ receptor as new substances to be possibly applied in the treatment of affective disorders. Identification of this novel 5-HT$_7$ receptor-mediated effect seems important to the elucidation of the physiological significance of these receptors. These studies provide new information about the involvement of 5-HT$_7$ receptors in the mechanisms which allow serotonin to simultaneously remodel neuronal activity in a functionally appropriate manner in a wide variety of cell types and excitatory and inhibitory circuits in the hippocampus.

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