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# IMPAIRED EFFECT OF ACTIVATION OF RAT HIPPOCAMPAL 5-HT$_7$ RECEPTORS, INDUCED BY TREATMENT WITH THE 5-HT$_7$ RECEPTOR ANTAGONIST SB 269970

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Effects of the 5-HT$_7$ receptor antagonist SB 269970, administered for 14 days (1.25 mg/kg), were studied in *ex vivo* slices of rat hippocampus. To activate the 5-HT$_7$ receptor, 5-carboxamidotryptamine (5-CT, 200 nM) was applied in the presence of WAY 100635 (2 μM), a 5-HT$_{1A}$ receptor antagonist. In contrast to control preparations, no 5-HT$_7$ receptor-mediated increase in excitability nor depolarization and an increase in the input resistance of CA1 and CA3 pyramidal neurons were present in slices prepared from rats treated with SB 269970. The treatment also abolished the stimulatory effect of 5-HT$_7$ receptor activation on spontaneous excitatory postsynaptic currents recorded from CA1 *stratum radiatum/lacunosum-moleculare* interneurons. These data demonstrate that repeated administration of SB 269970 impairs the reactivity of the CA1 hippocampal neuronal network to 5-HT$_7$ receptor activation.

Key words: *hippocampus, serotonin 5-HT$_7$ receptor, antagonist, pyramidal neurons, spontaneous excitatory postsynaptic current*

## INTRODUCTION

A widespread distribution of the 5-HT$_7$ receptor, the latest serotonin (5-HT) receptor subtype to be identified (1-3) in the brain (4, 5), underlies its involvement in various brain functions including circadian rhythmicity (6), sleep and wakefulness regulation (7) as well as learning and memory (8, 9). Recently the 5-HT$_7$ receptor has been shown to play an important role in neuronal plasticity of the mature brain (10).

A large body of experimental evidence suggests a causal link between alterations in the structure and function of the hippocampus and the pathophysiology of depression (11, 12). Exposure of experimental animals to uncontrollable, chronic stress induces depression-like symptoms including anorexia, weight loss, anhedonia, fatigue, impaired social interactions and memory dysfunctions (13). These effects are likely to be related to modifications in the function of several brain structures, however, a profound influence of stress on hippocampal synaptic transmission, plasticity and neuronal excitability appears to underly the stress-induced deficits in memory tests (14, 15).

While activation of the 5-HT$_7$ receptor exerts procognitive and antiamnestic effects (16), inactivation and blockade of the 5-HT$_7$ receptor have been shown to induce an anxiolytic and antidepressant-like action in animal models of anxiety and depression, including the elevated plus-maze test in rats and the forced swim and tail suspension tests in mice (17-20). The specific 5-HT$_7$ receptor antagonist SB 269970 and antidepressant drugs exert a synergistic action in the forced swim test in mice (21, 22). In addition, certain antidepressants may directly interact with the 5-HT$_7$ receptor (23), which also suggests that this receptor may constitute a novel target for the treatment of depression (24, 25). Hence, it has been postulated that 5-HT$_7$ receptor antagonists might be used for the treatment of depression, cognitive deficits and anxiety (24-26).

In the hippocampus, axon collaterals of CA3 pyramidal neurons provide the main excitatory input to CA1 principal pyramidal cells. The firing of the CA3 pyramidal neurons also recruits CA1 GABAergic interneurons and generates network oscillations in the CA1 area *via* feedforward and feedback inhibitory interactions (27-29). The activity of the hippocampal neuronal circuitry remains under the modulatory influence of 5-HT released from fibers originating in the median raphe nucleus (30-32). Activation of the 5-HT$_7$ receptor, present at high density in the hippocampus (4, 5) raises the excitability of neurons of the CA1 and CA3 areas through a decrease in the amplitude of slow afterhyperpolarization (sAHP) in CA3 pyramidal cells (33, 34) and a reduction of the slow afterhyperpolarization (sAHP) and frequency adaptation of action potential firing in CA1 pyramidal neurons (35, 36). The 5-HT$_7$ receptor also enhances the hyperpolarization-activated cation current $I_h$ in pyramidal cells (37). This receptor appears to be absent from the hippocampal interneurons (37). We have shown that administration of the 5-HT$_7$ receptor agonist does not influence the excitability of CA1 non-accommodating, fast-spiking GABAergic interneurons (38). We have also demonstrated that activation of 5-HT$_7$ receptors dose-dependently increases the frequency of spontaneous inhibitory postsynaptic currents (sIPSCs) recorded from CA1 pyramidal neurons (38).

However, in contrast to the effects of 5-HT$_7$ receptor activation, the mechanisms of the influence of 5-HT$_7$ receptor antagonists on neuronal activity and synaptic interactions in the

hippocampus are poorly understood. Using extracellular recording of bursting network activity in *ex vivo* hippocampal slices we have recently shown that repeated administration of SB 269970 to rats results in attenuation of the excitatory effects of 5-$HT_7$ receptors (39). In the present study, we aimed to establish the effects of treatment with SB 269970 on the reactivity of electrophysiologically identified major types of hippocampal neurons to 5-$HT_7$ receptor activation, as well as on the excitatory input to *stratum radiatum/lacunosum-moleculare* inhibitory interneurons.

## MATERIALS AND METHODS

### *Treatment of animals and preparation of hippocampal slices*

Experimental procedures were approved by the Animal Care and Use Committee at the Institute of Pharmacology, Polish Academy of Sciences, and were carried out in accordance with the "Principles of Laboratory Animal Care" (NIH publication no. 85-23, revised 1985) and the national law. Male Wistar rats, weighing approx. 140 g at the beginning of the experiment, were housed in groups on a controlled light/dark cycle (the light on: 7.00–19.00). The rats had free access to standard food and tap water. The rats from the experimental group (n=10) received (2R)-1-[(3-hydroxyphenyl)sulfonyl]-2-[2-(4-methyl-1-piperidinyl)ethyl]pyrrolidine hydrochloride (SB 269970; 1.25 mg/kg i.p., dissolved in 0.9% NaCl, volume: 1 ml/kg) once daily for 14 days. The animals from the control group (n=10) received 0.9% NaCl only.

Two days after the last injection the rats were anesthetized with isoflurane and were then decapitated. Their brains were quickly removed and placed in an ice-cold (0°C) artificial cerebrospinal fluid (ACSF), composed of (in mM) NaCl (130), KCl (5), $CaCl_2$ (2.5), $MgSO_4$ (1.3), $KH_2PO_4$ (1.25), $NaHCO_3$ (26) and D-glucose (10) and bubbled with a mixture of 95% $O_2$ - 5% $CO_2$. Transverse hippocampal slices (thickness: 420 µm) were cut using a vibrating microtome (Leica VT1000) and were then stored submerged in ACSF at 32 ± 0.5°C.

### *Whole-cell recording*

After at least 3 hours of preincubation, a slice was placed in the recording chamber superfused at 2.5 ml/min with warm (32 ± 0.5°C), modified ACSF composed of (in mM) NaCl (132), KCl (2), $KH_2PO_4$ (1.25), $NaHCO_3$ (26), $MgSO_4$ (1.3), $CaCl_2$ (2.5) and D-glucose (10), bubbled with 95% $O_2$ - 5% $CO_2$. Neurons were visualized using the Zeiss Axioskop 2 upright microscope (Nomarski optics), a 40 × water immersion lens and an infrared camera (35). Patch pipettes were pulled from borosilicate glass capillaries (Clark Electromedical Instruments) using the Sutter Instrument P87 puller and were then filled with a solution containing (in mM) 130 K-gluconate, 5 NaCl, 0.3 $CaCl_2$, 2 $MgCl_2$, 10 HEPES, 5 $Na_2$-ATP, 0.4 Na-GTP, and 1 EGTA (osmolarity: 290 mOsm, pH = 7.2; 40). The pipettes had an open tip resistance of approx. 6 MΩ.

Signals were recorded from CA1 and CA3 pyramidal neurons and CA1 *stratum radiatum/lacunosum-moleculare* interneurons using the MultiClamp 700B amplifier and were digitized at 20 kHz using the Digidata 1400 interface (Molecular Devices, USA). Neurons were distinguished on the basis of the morphology of the cell body and the responses to a series of hyper- and depolarizing current pulses (38). Spontaneous excitatory postsynaptic currents (sEPSCs) were recorded for 8 min as inward currents at a holding potential of –76 mV, as described previously (40). Individual events were detected off-line and analyzed using the Mini Analysis software (Synaptosoft, USA). Data were accepted for analysis when the access resistance ranged between 15-18 MΩ and was stable (<25% change) during the recording.

To activate 5-$HT_7$ receptors, 200 nM 5-carboxamidotryptamine (5-CT, Tocris), an agonist of 5-$HT_{1A}$ and 5-$HT_7$ receptors, was added to the modified ACSF for 15 min in the presence of 2 µM N-[2-[4-(2-methoxyphenyl)-1piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide (WAY 100635, Sigma Aldrich), a selective 5-$HT_{1A}$ receptor antagonist, which was introduced at least 20 min earlier (35, 41).

### *Statistical analysis*

Statistical analysis was carried out using unpaired or paired Student's *t* tests. The data are presented as the mean ± S.E.M.

## RESULTS

### *Repeated administration of SB 269970 abolishes the effects of 5-$HT_7$ receptor activation in pyramidal neurons*

To test the effects of 5-$HT_7$ receptor activation on the intrinsic excitability of pyramidal cells, a series of depolarizing current pulses (500 ms) were applied before and again after addition of 5-CT (an agonist of 5-$HT_7$ and 5-$HT_{1A}$ receptors; 42) to the ACSF (in the presence of WAY 100635 to block 5-$HT_{1A}$ receptors). In the slices obtained from control animals, activation of the 5-$HT_7$ receptor increased the number of spikes generated by the injected current in both CA1 (*Fig. 1A$_{1-4}$*) and CA3 (*Fig. 2A$_{1-4}$*) pyramidal neurons. That effect was most prominent at low values of current intensity, while at its high values the number of spikes generated for a given current before and after addition of 5-CT was similar. The 5-$HT_7$ receptor-mediated change in the intrinsic excitability (gain)- of pyramidal neurons was more substantial in CA3 compared to CA1 cells (58.3 ± 5.9% vs. 32.6 ± 3.6%, respectively; the mean ±S.E.M., $P<0.05$, t-test). However, in the slices prepared from rats injected with SB 269970, the application of 5-CT did not result in an increase in excitability (*Figs. 1B$_{1-4}$*, and *2B$_{1-4}$*). In control preparations, activation of the 5-$HT_7$ receptor resulted in a small depolarization and an increase in the input resistance of CA1 and CA3 pyramidal cells as well (*Table 1*) . Those effects were absent from neurons obtained from SB 269970-treated rats. Treatment with SB 269970 did not affect the basic membrane properties of CA1 and CA3 pyramidal cells (*Table 1*).

### *Repeated administration of SB 269970 abolishes the effect of 5-$HT_7$ receptor activation on sEPSCs recorded from GABAergic interneurons*

Spontaneous EPSCs were recorded from CA1 *stratum radiatum/lacunosum-moleculare* fast-spiking interneurons (*Fig. 3*). Basic membrane properties of these cells are summarized in *Table 2*. The mean frequency of sEPSCs recorded in the standard ACSF (termed: baseline frequency) was not significantly different in the interneurons obtained from control rats compared to those from rats receiving SB 269970 (*Table 2*). 5-CT application (in the presence of WAY 100635) increased the mean frequency of sEPSCs in control preparations (*Figs. 3B$_1$* and *C*, *Table 2*). However, in slices prepared from rats receiving SB 269970, application of 5-CT did not result in an increase in the mean frequency of sEPSCs (*Figs. 3B$_2$* and *C*, *Table 2*). Activation of 5-$HT_7$ receptors remained without effect on the mean amplitude of sEPSCs in both control slices and slices prepared from rats receiving SB 269970 (*Fig. 3D*, *Table 2*).

Activation of 5-$HT_7$ receptors affected the excitability of recorded interneurons in neither control slices nor slices

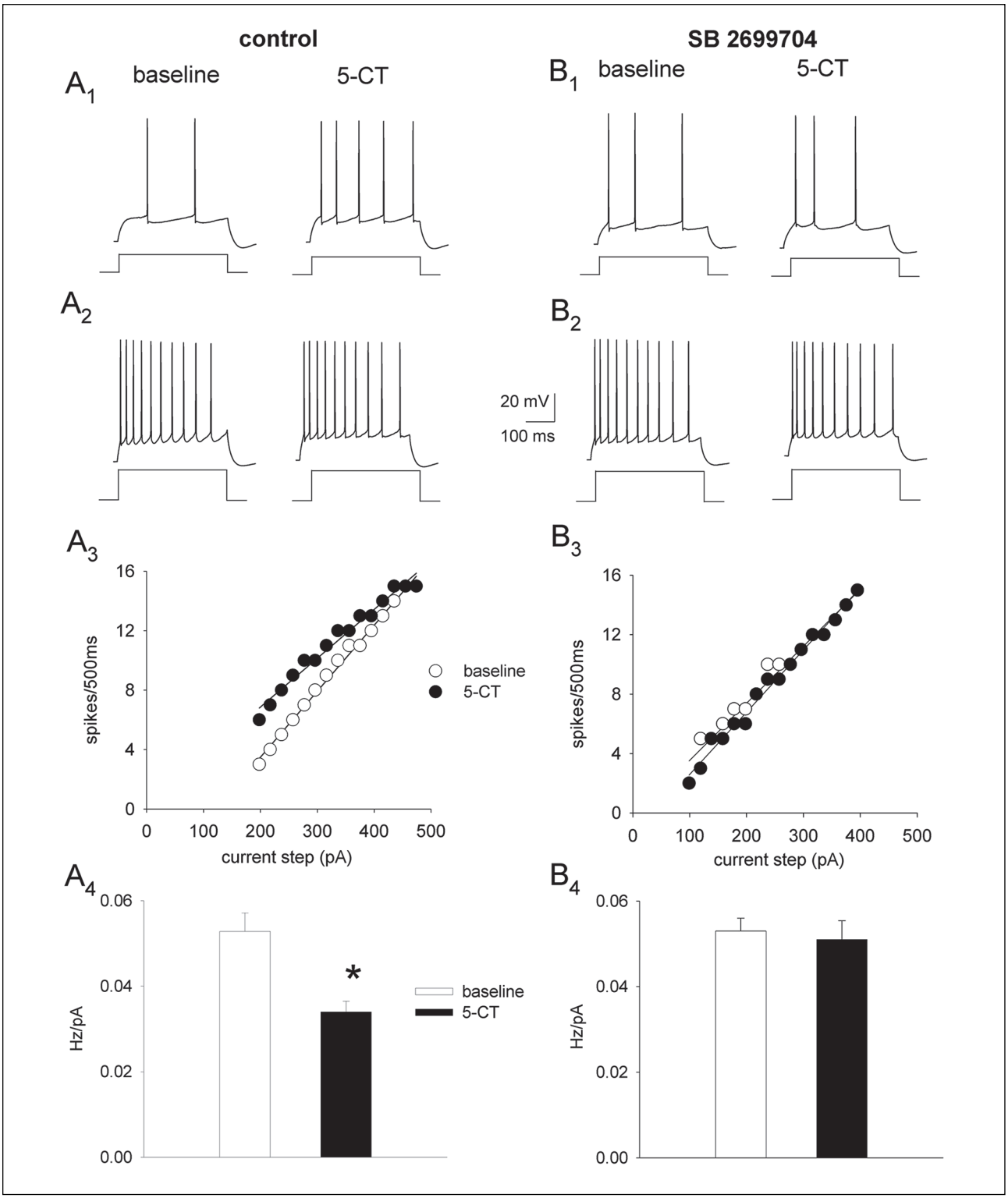


*Fig. 1.* The lack of effect of 5-HT$_7$ receptor activation on the excitability of CA1 pyramidal neurons after treatment with SB 269970. (*A$_1$*) A typical example of the response of a pyramidal cell obtained from a control rat to a depolarizing current pulse (250 pA) under baseline conditions (to the left), and after addition of 5-CT to ACSF (to the right). (*A$_2$*) An example of a response at a higher stimulation intensity (500 pA) before and after addition of 5-CT. (*A$_3$*) The injected current vs. spiking rate relationship in a representative control cell before (baseline recording; open circles) and after application of 5-CT (filled circles). Solid lines represent linear fits to the experimental data. (*A$_4$*) The mean (± S.E.M.) slope (i.e. gain) of the current vs. spiking rate relationship under baseline conditions (open bar) and after application of 5-CT (filled bar; n=19 cells; * P<0.05, paired t - test). (*B$_1$* and *B$_2$*) Typical examples of responses to depolarizing current pulses (250 and 500 pA) under baseline conditions and after addition of 5-CT to ACSF in a slice obtained from a rat treated with SB 269970. (*B$_3$*) The injected current vs. spiking rate relationship in a representative cell from a treated rat before (open circles) and after application of 5-CT (black circles). Continuous lines represent linear fits to the experimental data. (*B$_4$*) Mean (± S.E.M.) slope of the current vs. spiking rate relationship under baseline conditions (open bar) and after application of 5-CT in 19 cells obtained from SB 269970-treated rats (filled bar). The difference is not statistically significant.

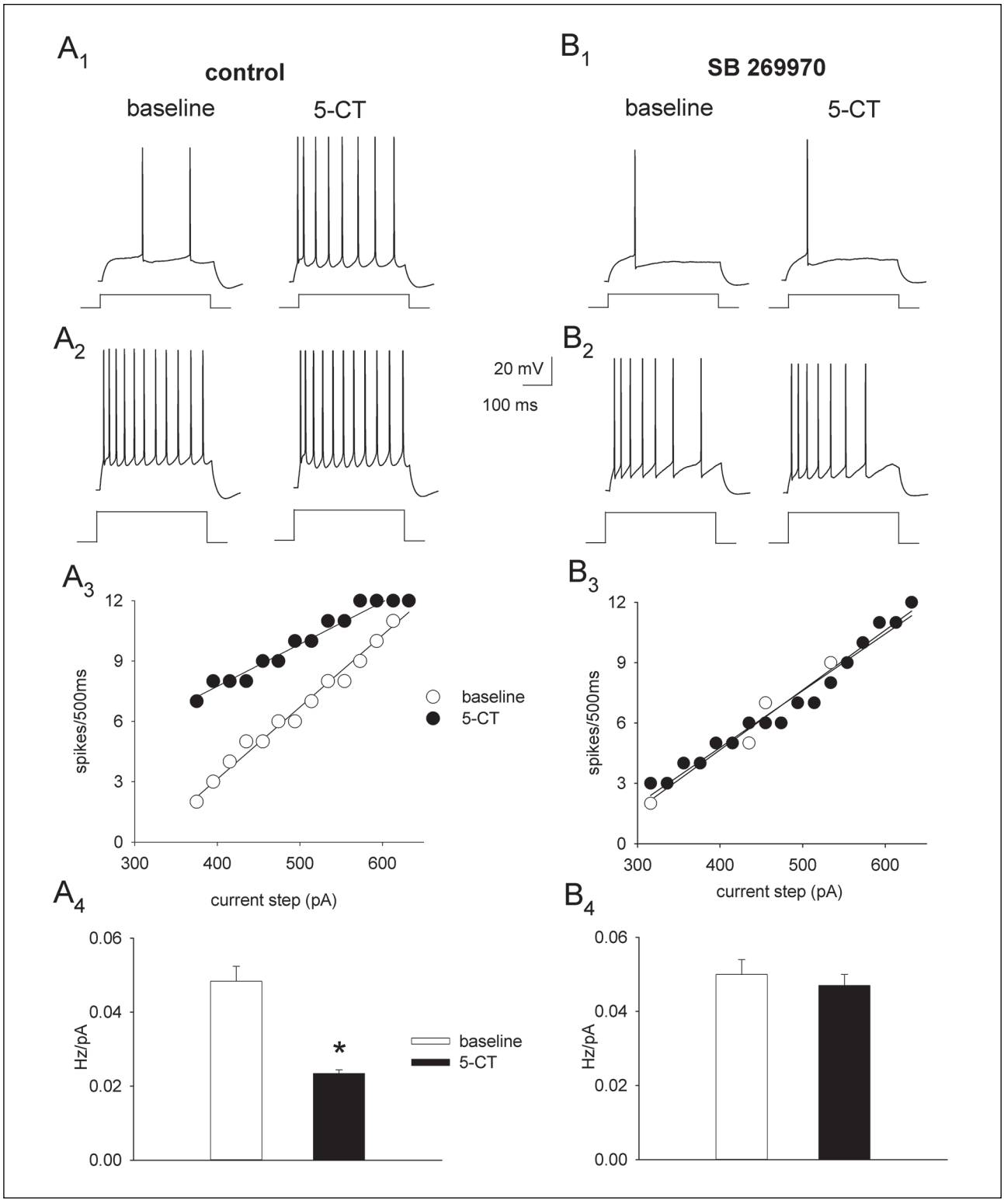


*Fig. 2.* The lack of effect of 5-HT$_7$ receptor activation on the excitability of CA3 pyramidal neurons after treatment with SB 269970. ($A_{1\text{-}3}$) Examples of the responses of a control cell. ($B_{1\text{-}3}$) Examples of responses of a cell obtained after treatment with SB 269970. ($A_4$ and $B_4$) The mean (± S.E.M.) slope of the current vs. spiking rate relationship of pyramidal cells in baseline conditions (open bars) and after application of 5-CT (filled bars) in control slices ($A_4$, n=7) and slices obtained after treatment with SB 269970 ($B_4$, n=8). All labels as in *Fig. 1*.

prepared from rats receiving SB 269970, as the mean slope (gain) of the current versus the spiking rate relationship in interneurons originating from treated and control animals was similar (*Fig. 3E*).

## DISCUSSION

The results of the present study indicate that treatment of rats with the specific 5-HT$_7$ receptor antagonist SB 269970 abolishes

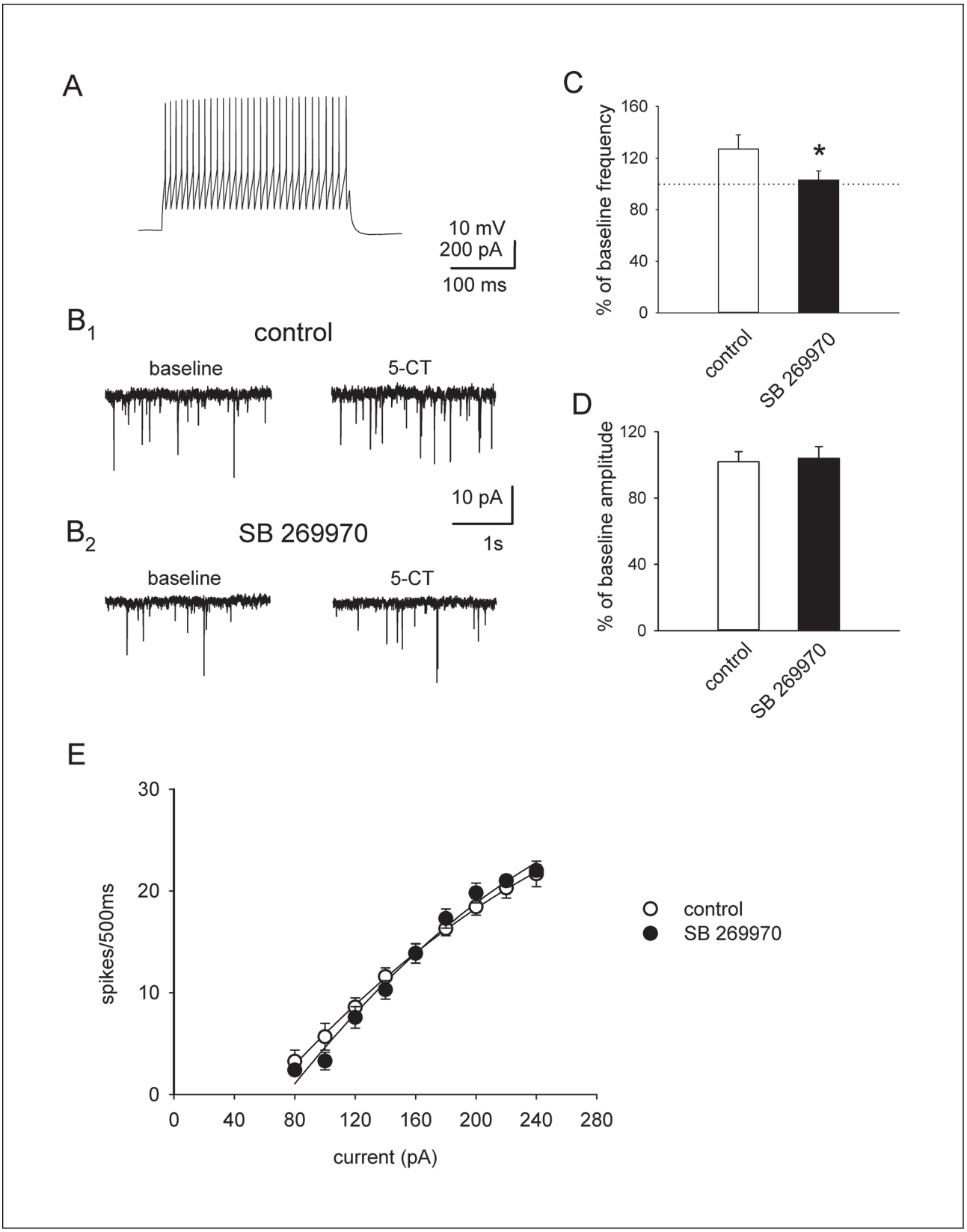


*Fig. 3.* The influence of 5-HT$_7$ receptor activation on spontaneous EPSCs recorded from fast-spiking interneurons. (*A*) An example of the responses of a representative control interneuron to a depolarizing current pulse. (*B$_{1-2}$*) Examples of raw recordings of sEPSCs before (baseline, left trace) and after (right trace) application of 5-CT from interneurons in a control slice (*B$_1$*) and in a slice prepared from a rat receiving injections of SB 269970 (*B$_2$*). (*C*) Application of 5-CT increases the mean frequency (± S.E.M.) of sEPSCs in control interneurons (open bar, n=18) but not in cells obtained from rats receiving injections of SB 269970 (filled bar, n=15). * P<0.05, t - test). (*D*) Application of 5-CT influences the amplitude of sEPSCs in neither control nor SB 269970-treated preparations; the means ± S.E.M. (*E*) The injected current vs. spiking rate relationship (the mean ± S.E.M.) in control cells (open circles) and interneurons originating from rats receiving SB 269970 (filled circles).

*Table 1.* Basic membrane properties of CA1 and CA3 pyramidal neurons and the effects of 5-$HT_7$ receptor activation in slices obtained from control rats and animals treated with SB 269970.

| | | control | | SB 269970 | |
|---|---|---|---|---|---|
| | | baseline | in 5-CT | baseline | in 5-CT |
| CA1 | Resting membrane potential $V_m$ (mV) | –64.1 ± 0.4 | –62.9 ± 0.5* | –63.7 ± 0.4 | –63.3 ± 0.5 |
| | Input resistance $R_m$ (MΩ) | 68.4 ± 4.5 | 83.1 ± 6.8*** | 58.2 ± 3.4 | 60.7 ± 6.0 |
| | n | 19 | | 19 | |
| CA3 | Resting membrane potential $V_m$ (mV) | –63.2 ± 0.4 | –60.4 ± 0.2** | –63.8 ± 0.8 | –63.3 ± 0.9 |
| | Input resistance $R_m$ (MΩ) | 77.6 ± 13.8 | 99.5 ± 12.0*** | 81.7 ± 20.0 | 84.4 ± 18.7 |
| | n | 7 | | 8 | |

The data are presented as the mean ± S.E.M. Baseline, the data obtained before addition of 5-CT to the ACSF; in 5-CT, the data obtained after addition of 5-CT to the ACSF. * P<0.05, ** P<0.01, *** P<0.001; paired t - test. The differences between baseline values in the control and the SB 269970 group are not significant.

*Table 2.* Basic membrane properties and the effects of 5-$HT_7$ receptor activation on sEPSCs recorded from fast-spiking interneurons in slices obtained from control rats and animals treated with SB 269970.

| | | control | SB 269970 |
|---|---|---|---|
| Resting membrane potential $V_m$ (mV) | | –69.2 ± 3.1 | –70.3 ± 4.4 |
| Input resistance $R_m$ (MΩ) | | 187.8 ± 34.6 | 192.1 ± 33.9 |
| Mean frequency of sEPSCs (Hz) | baseline | 2.36 ± 0.5 | 1.67 ± 0.4 |
| | 5-CT | 2.98 ± 0.5** | 1.72 ± 0.5 |
| Mean amplitude of sEPSCs (pA) | baseline | 11.60 ± 1.2 | 13.05 ± 1.4 |
| | 5-CT | 11.71 ± 1.2 | 12.90 ± 1.4 |
| n | | 18 | 15 |

The data are presented as the mean ± S.E.M. ** P≤0.01 (baseline vs. 5-CT; paired t - test).

the effects of 5-$HT_7$ receptor activation on the intrinsic excitability of hippocampal pyramidal neurons. It is noteworthy that some studies that used expression systems allowing detection of the constitutive activity of the 5-$HT_7$ receptor described SB 269970 as an inverse agonist (e.g. 43). The constitutive activity of the 5-$HT_7$ receptor appears to be regulated by palmitoylation of the C-terminal domain of the receptor protein (44).

In slices obtained from untreated rats, addition of 200 nM 5-CT to the ACSF containing 2 μM WAY 100636 resulted in an increased number of spikes generated in CA1 and CA3 pyramidal neurons by lower intensity depolarizing current pulses, a change in the resting membrane potential and an increase in the input resistance. These observations are consistent with some earlier studies which demonstrated that activation of the 5-$HT_7$ receptor decreased $K^+$ conductances and increased the $I_h$ current, thus raising the excitability of hippocampal pyramidal cells (33, 35, 37). Interestingly, the effect of 5-$HT_7$ receptor activation was stronger in CA3 compared to CA1 pyramidal cells which potentially may have resulted from a greater 5-$HT_7$ receptor density in the CA3 area (4, 45). Such effects of 5-$HT_7$ receptor activation were absent from slices prepared from rats treated with SB 269970. We have recently demonstrated that treatment of rats with SB 269970 following a regime identical to that used in the present study results in attenuation, but not abolishment, of the excitatory effects of 5-$HT_7$ receptor activation on extracellularly-recorded, spontaneous network activity which can be induced in hippocampal slices by incubation in the $Mg^{2+}$-free ACSF (39). Moreover, in slices prepared from SB 269970-treated rats, the basal frequency of spontaneous bursts has been found to be lower than in control preparations (39). In the present study, no significant difference in the frequency of spontaneous EPSCs was observed in interneurons obtained from SB 269970-treated and control rats. It is noteworthy that in the present study the recordings were performed under conditions that effectively prevented the occurrence of NMDA receptor-mediated postsynaptic currents. Thus, the differences in the experimental conditions during recording are likely to account for such an apparent discrepancy.

We previously demonstrated that SB 269970, administered for 14 days, induced a decrease in the maximum density ($B_{max}$) of 5-$HT_7$ receptors in rat hippocampus without changing their mean affinity for [$^3$H]-SB 269970 (39). Moreover, treatment with SB 269970 resulted in a decrease in the expression level of mRNAs for $G\alpha_s$ and $G\alpha_{12}$ proteins (39), which are known to be activated by the 5-$HT_7$ receptor and to mediate its actions (46). Hence, the present findings are consistent with the treatment-induced reduction in the amount of available 5-$HT_7$ receptors and the impairment of 5-$HT_7$ receptor-activated intracellular signaling cascades in the cytoplasm of pyramidal neurons.

The present data confirm our earlier findings that application of 5-CT in the presence of WAY 100635 increased the frequency of sEPSCs recorded from fast-spiking *stratum radiatum/lacunosum-moleculare* interneurons, but did not influence the excitability of those cells (38). The present results also demonstrate that the 5-$HT_7$ receptor-mediated increase in the frequency of sEPSCs recorded from fast-spiking interneurons does not occur in slices obtained from SB 269970-treated animals. This observation is consistent with the fact that CA1 interneurons receive excitatory connections from CA1 and CA3 pyramidal neurons (47). These cells lose the reactivity to 5-$HT_7$ receptor activation after treatment with SB 269970 (present study). Since GABAergic interneurons modulate the activity of pyramidal neurons, treatment with SB 269970 should result in a lack of 5-$HT_7$ receptor-mediated enhancement of the GABAergic input to CA1 pyramidal cells, under normal conditions being an indirect consequence of the increased excitatory input to GABAergic interneurons due to activation of 5-$HT_7$ receptors located on glutamatergic cells (35, 38).

Experimental evidence supports the involvement of abnormalities in the GABAergic inhibition in the development of neuropsychiatric diseases such as schizophrenia, autism and depression (48-52). Some data also suggest that alterations in the adequate balance and correct integration of the GABAergic transmission originating from diverse interneuron sources may lead to the development of depression (53, 54). There also exists some experimental evidence that antidepressant drugs can modulate GABAergic transmission in the hippocampus through modifications of the monoaminergic tone (55, 56) or a direct modulation of $GABA_A$ receptors (57) or, finally, through changes in GABA release, not involving monoaminergic transmission (53, 58).

Treatment of rats with antidepressant drugs attenuates the excitatory effects of activation of the 5-$HT_7$ receptor in the hippocampus (41). Similar effects are induced by treatment with the 5-$HT_7$ receptor antagonist SB 269970 (39, present study). Summing up, the above data support the hypothesis that the phenomenon of the functional desensitization of 5-$HT_7$ receptor system, which leads to alterations in GABAergic transmission, may represent one of the mechanisms of action of antidepressants (24, 59) and the antidepressant action of 5-$HT_7$ antagonists.

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Conflict of interests: None declared.

## REFERENCES

1. Bard JA, Zgombick J, Adham N, Vaysse P, Branchek TA, Weinshank RL. Cloning of a novel human serotonin receptor (5-$HT_7$) positively linked to adenylate cyclase. *J Biol Chem* 1993; 268: 23422-23426.
2. Ruat M, Traiffort E, Leurs R, *et al.* Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-$HT_7$) activating cAMP formation. *Proc Natl Acad Sci USA* 1993; 90: 8547-8551.
3. Hedlund PB, Sutcliffe JG. Functional, molecular and pharmacological advances in 5-$HT_7$ receptor research. *Trends Pharmacol Sci* 2004; 25: 481-486.
4. Gustafson EL, Durkin MM, Bard JA, Zgombick J, Branchek TA. A receptor autoradiographic and in situ hybridization analysis of the distribution of the 5-$HT_7$ receptor in rat brain. *Br J Pharmacol* 1996; 117: 657-666.
5. Bonaventure P, Nepomuceno D, Kwok A, *et al.* Reconsideration of 5-hydroxytryptamine (5-HT)(7) receptor distribution using [(3)H]5-carboxamidotryptamine and [(3)H]8-hydroxy-2-(di-n-propylamino)tetraline: analysis in brain of 5-HT(1A) knockout and 5-HT(1A/1B) double-knockout mice. *J Pharmacol Exp Ther* 2002; 302: 240-248.
6. Rea MA. Photic entrainment of circadian rhythms in rodents. *Chronobiol Int* 1998; 15: 395-423.
7. Monti JM, Jantos H. The role of serotonin 5-$HT_7$ receptor in regulating sleep and wakefulness. *Rev Neurosci* 2014; 25: 429-437.
8. Roberts AJ, Hedlund PB. The 5-HT(7) receptor in learning and memory. *Hippocampus* 2012; 22: 762-771.
9. Gasbarri A, Pompili A. Serotonergic 5-$HT_7$ receptors and cognition. *Rev Neurosci* 2014; 25: 311-323.
10. Volpicelli F, Speranza L, di Porzio U, Crispino M, Perrone-Capano C. The serotonin receptor 7 and the structural plasticity of brain circuits. *Front Behav Neurosci* 2014; 8: 318.
11. Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. *Nat Rev Neurosci* 2011; 12: 467-477.
12. Willner P, Scheel-Kruger J, Belzung C. The neurobiology of depression and antidepressant action. *Neurosci Biobehav Rev* 2013; 37: 2331-2371.
13. Koo JW, Duman RS. Evidence for IL-1 receptor blockade as a therapeutic strategy for the treatment of depression. *Curr Opin Investig Drugs* 2009; 10: 664-671.
14. Joels M. Impact of glucocorticoids on brain function: relevance for mood disorders. *Psychoneuroendocrinology* 2011; 36: 406-414.
15. Musazzi L, Racagni G, Popoli M. Stress, glucocorticoids and glutamate release: effects of antidepressant drugs. *Neurochem Int* 2011; 59: 138-149. \
16. Meneses A, Perez-Garcia G, Liy-Salmeron G, Ponce-Lopez T, Lacivita E, Leopoldo M. 5-$HT_7$ receptor activation: procognitive and antiamnesic effects. *Psychopharmacology* (*Berl*) 2015; 232: 595-603.
17. Wesolowska A, Kowalska M. Influence of serotonin 5-HT(7) receptor blockade on the behavioral and neurochemical effects of imipramine in rats. *Pharmacol Rep* 2008; 60: 464-474.
18. Guscott M, Bristow LJ, Hadingham K, *et al.* Genetic knockout and pharmacological blockade studies of the 5-$HT_7$ receptor suggest therapeutic potential in depression. *Neuropharmacology* 2005; 48: 492-502.
19. Hedlund PB, Huitron-Resendiz S, Henriksen SJ, Sutcliffe JG. 5-$HT_7$ receptor inhibition and inactivation induce antidepressantlike behavior and sleep pattern. *Biol Psychiatry* 2005; 58: 831-837.
20. Wesolowska A, Nikiforuk A, Stachowicz K, Tatarczynska E. Effect of the selective 5-HT(7) receptor antagonist SB 269970 in animal models of anxiety and depression. *Neuropharmacology* 2006; 51: 578-586.
21. Bonaventure P, Kelly L, Aluisio L, *et al.* Selective blockade of 5-hydroxytryptamine (5-HT)7 receptors enhances 5-HT transmission, antidepressant-like behavior, and rapid eye movement sleep suppression induced by citalopram in rodents. *J Pharmacol Exp Ther* 2007; 321: 690-698.
22. Wesolowska A, Tatarczynska E, Nikiforuk A, Chojnacka-Wojcik E. Enhancement of the anti-immobility action of antidepressants by a selective 5-$HT_7$ receptor antagonist in the forced swimming test in mice. *Eur J Pharmacol* 2007; 555: 43-47.
23. Mullins UL, Gianutsos G, Eison AS. Effects of antidepressants on 5-$HT_7$ receptor regulation in the rat hypothalamus. *Neuropsychopharmacology* 1999; 21: 352-367.

24. Hedlund PB. The 5-$HT_7$ receptor and disorders of the nervous system: an overview. *Psychopharmacology* 2009; 206: 345-354.
25. Mnie-Filali O, Lambas-Senas L, Scarna H, Haddjeri N. Therapeutic potential of 5-$HT_7$ receptors in mood disorders. *Curr Drug Targets* 2009; 10: 1109-1117.
26. Leopoldo M, Lacivita E, Berardi F, Perrone R, Hedlund PB. Serotonin 5-$HT_7$ receptor agents: structure-activity relationships and potential therapeutic applications in central nervous system disorders. *Pharmacol Ther* 2011; 129: 120-148.
27. Allen K, Monyer H. Interneuron control of hippocampal oscillations. *Curr Opin Neurobiol* 2014; 31C: 81-87.
28. Klausberger T, Somogyi P. Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. *Science* 2008; 321: 53-57.
29. Zemankovics R, Veres JM, Oren I, Hajos N. Feedforward inhibition underlies the propagation of cholinergically induced gamma oscillations from hippocampal CA3 to CA1. *J Neurosci* 2013; 33: 12337-12351.
30. Bonvento G, Scatton B, Claustre Y, Rouquier L. Effect of local injection of 8-OH-DPAT into the dorsal or median raphe nuclei on extracellular levels of serotonin in serotonergic projection areas in the rat brain. *Neurosci Lett* 1992; 137: 101-104.
31. Freund TF, Gulyas AI, Acsady L, Gorcs T, Toth K. Serotonergic control of the hippocampus via local inhibitory interneurons. *Proc Natl Acad Sci USA* 1990; 87: 8501-8505.
32. Moore RY, Halaris AE, Jones BE. Serotonin neurons of the midbrain raphe: ascending projections. *J Comp Neurol* 1978; 180: 417-438.
33. Bacon WL, Beck SG. 5-Hydroxytryptamine7 receptor activation decreases slow afterhyperpolarization amplitude in CA3 hippocampal pyramidal cells. *J Pharmacol Exp Ther* 2000; 294: 672-679.
34. Gill CH, Soffin EM, Hagan JJ, Davies CH. 5-$HT_7$ receptors modulate synchronized network activity in rat hippocampus. *Neuropharmacology* 2001; 42: 82-92.
35. Tokarski K, Zahorodna A, Bobula B, Hess G. 5-$HT_7$ receptors increase the excitability of rat hippocampal CA1 pyramidal neurons. *Brain Res* 2003; 993: 230-234.
36. Ciranna L, Catania MV. 5-$HT_7$ receptors as modulators of neuronal excitability, synaptic transmission and plasticity: physiological role and possible implications in autism spectrum disorders. *Front Cell Neurosci* 2014; 8: 250.
37. Bickmeyer U, Heine M, Manzke T, Richter DW. Differential modulation of I(h) by 5-HT receptors in mouse CA1 hippocampal neurons. *Eur J Neurosci* 2002; 16: 209-218.
38. Tokarski K, Kusek M, Hess G. 5-$HT_7$ receptors modulate GABAergic transmission in rat hippocampal CA1 area. *J Physiol Pharmacol* 2011; 62: 535-540.
39. Tokarski K, Zelek-Molik A, Duszynska B, *et al.* Acute and repeated treatment with the 5-$HT_7$ receptor antagonist SB 269970 induces functional desensitization of 5-$HT_7$ receptors in rat hippocampus. *Pharmacol Rep* 2012; 64: 256-265.
40. Kusek M, Tokarski K, Hess G. Repeated restraint stress enhances glutamatergic transmission in the paraventricular nucleus of the rat hypothalamus. *J Physiol Pharmacol* 2013; 64: 565-570.
41. Tokarski K, Zahorodna A, Bobula B, Grzegorzewska M, Pitra P, Hess G. Repeated administration of citalopram and imipramine alters the responsiveness of rat hippocampal circuitry to the activation of 5-$HT_7$ receptors. *Eur J Pharmacol* 2005; 524: 60-66.
42. Thomas DR, Middlemiss DN, Taylor SG, Nelson P, Brown AM. 5-CT stimulation of adenylyl cyclase activity in guinea-pig hippocampus: evidence for involvement of 5-$HT_7$ and 5-HT1A receptors. *Br J Pharmacol* 1999; 128: 158-164.
43. Romero G, Pujol M, Pauwels PJ. Reanalysis of constitutively active rat and human 5-$HT_7$(a) receptors in HEK-293F cells demonstrates lack of silent properties for reported neutral antagonists. *Naunyn Schmiedebergs Arch Pharmacol* 2006; 374: 31-39.
44. Kvachnina E, Dumuis A, Wlodarczyk J, *et al.* Constitutive Gs-mediated, but not G12-mediated, activity of the 5-hydroxytryptamine 5-$HT_7$(a) receptor is modulated by the palmitoylation of its C-terminal domain. *Biochim Biophys Acta* 2009; 1793: 1646-1655.
45. Yau JL, Noble J, Secki JR. Acute restraint stress increases 5-$HT_7$ receptor mRNA expression in the rat hippocampus. *Neurosci Lett* 2001; 309: 141-144.
46. Vanhoenacker P, Haegeman G, Leysen JE. 5-$HT_7$ receptors: current knowledge and future prospects. *Trends Pharmacol Sci* 2000; 21: 70-77.
47. Somogyi P, Klausberger T. Defined types of cortical interneurone structure space and spike timing in the hippocampus. *J Physiol* 2005; 562: 9-26.
48. Benes FM, Berretta S. GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology* 2001; 25: 1-27.
49. Levitt P, Eagleson KL, Powell EM. Regulation of neocortical interneuron development and the implications for neurodevelopmental disorders. *Trends Neurosci* 2004; 27: 400-406.
50. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci* 2005; 6: 312-324.
51. Orekhova EV, Stroganova TA, Nygren G, *et al.* Excess of high frequency electroencephalogram oscillations in boys with autism. *Biol Psychiatry* 2007; 62: 1022-1029.
52. Sanacora G, Saricicek A. GABAergic contribution to the pathophysiology of depression and mechanism of antidepressant action. *CNS Neurol Disord Drug Targets* 2007; 6: 127-140.
53. Mendez P, Pazienti A, Szabo G, Bacci A. Direct alteration of a specific inhibitory circuit of the hippocampus by antidepressants. *J Neurosci* 2012; 32: 16616-16628.
54. Smith KS, Rudolph U. Anxiety and depression: mouse genetics and pharmacological approaches to the role of GABA(A) receptor subtypes. *Neuropharmacology* 2012; 62: 54-62.
55. Bijak M, Misgeld U. Effects of serotonin through serotonin1A and serotonin4 receptors on inhibition in the guinea-pig dentate gyrus in vitro. *Neuroscience* 1997; 78: 1017-1026.
56. Piotrowska A, Siwek A, Wolak M, *et al.* Involvement of the monoaminergic system in the antidepressant-like activity of chromium chloride in the forced swim test. *J Physiol Pharmacol* 2013; 64: 493-498.
57. Robinson RT, Drafts BC, Fisher JL. Fluoxetine increases GABA(A) receptor activity through a novel modulatory site. *J Pharmacol Exp Ther* 2003; 304: 978-984.
58. Wabno J, Hess G. Repeated administration of imipramine modifies GABAergic transmission in rat frontal cortex. *J Neural Transm* 2013; 120, 711-719.
59. Tokarski K, Bobula B, Grzegorzewska-Hiczwa M, Kusek M, Hess G. Stress- and antidepressant treatment-induced modifications of 5-$HT_7$ receptor functions in the rat brain. *Pharmacol Rep* 2012; 64: 1305-1315.

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