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Comparison of the Effects of Serotonin in the Hippocampus and the Entorhinal Cortex

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Abstract

Among the molecular, cellular, and systemic events that have been proposed to modulate the function of the hippocampus and the entorhinal cortex (EC), one of the most frequently cited possibilities is the activation of the serotonergic system. Neurons in the hippocampus and in the EC receive a strong serotonergic projection from the raphe nuclei and express serotonin (5-HT) receptors at high density. Here we review the various effects of 5-HT on intrinsic and synaptic properties of neurons in the hippocampus and the EC. Although similar membrane-potential changes following 5-HT application have been reported for neurons of the entorhinal cortex and the hippocampus, the effects of serotonin on synaptic transmission are contrary in both areas. Serotonin mainly depresses fast and slow inhibition of the principal output cells of the hippocampus, whereas it selectively suppresses the excitation in the entorhinal cortex. On the basis of these data, we discuss the possible role of serotonin under physiological and pathophysiological circumstances.

Index Entries: Serotonin; hippocampus; CA1; entorhinal cortex; intrinsic properties; synaptic transmission; EPSP/Cs; IPSP/Cs; presynaptic.

Introduction

On a cellular level, we can divide the effects of serotonin into modulations of intrinsic and synaptic (pre- or postsynaptic) properties of neurons. Menahem Segal was one of the first to describe the effects of serotonin on intrinsic properties of CA1 pyramidal cells (1980). Reports by Andrade and Nicoll (1987) and Colino and Halliwell (1987) a few years later, added interesting insights in the differential modulation of K^+-currents by serotonin. Later on, it was found that serotonin also influences synaptic transmission in the hippocampus (Ghadimi et al., 1994; Jahnsen, 1980; Oleskevich and Lacaille, 1992; Segal, 1990). A number

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of in vitro and in vivo studies suggest that serotonin can have both excitatory and inhibitory effects on different cells (Andrade and Nicoll, 1987; Colino and Haliwell, 1987; Segal, 1980; 1990; Sogita et al., 1992; Yakel and Jackson, 1988). Most likely, this functional diversity results from the differential expression of serotonin receptor subtypes (Andrade and Chaput, 1991; Andrade and Nicoll, 1987; Beck, 1992; Chaput et al., 1990; Maricq et al., 1991; Sugita et al., 1992; Yakel and Jackson, 1988).

Altogether, the intrinsic and synaptic modulation by 5-HT may result in altered network properties of the hippocampal-entorhinal system. Serotonergic inputs to the hippocampus and the entorhinal cortex from the raphe nuclei are involved in the modulation of "theta" oscillations (Assaf and Miller, 1978; Vanderwolf, 1988). These inputs are not only thought to be important for the functional spatial learning behavior (Richter-Levin et al., 1993; 1994), but they are also involved in various forms of diseases such as certain subforms of schizophrenia (Kinon and Lieberman, 1996; Maurel Remy et al., 1995) and temporal-lobe epilepsy (Schmitz et al., 1997; Wada et al., 1992a,b; 1993).

This article will briefly compare the effects of serotonin in the hippocampus and the entorhinal cortex, with special emphasis on intrinsic and synaptic properties at the cellular level.

Effects of Serotonin on Intrinsic Properties

Effects in the Hippocampus

Serotonin directly hyperpolarizes pyramidal cells through the activation of 5-HT_{1A} receptors (Andrade and Nicoll, 1987; Colino and Haliwell, 1987; Schmitz et al., 1995; Segal et al., 1989) (*see* Fig. 1). The hyperpolarization results from opening of Ca^{2+} independent K^+ channels and leads to a decrease in unit firing in vivo (Richter-Levin and Segal, 1992). A number of observations indicate, however, that serotonin can also increase neuronal excitability in the hippocampus. Population-spike amplitudes recorded in vivo from the dentate gyrus were increased by 5-HT (Klancnik et al., 1989) and transient increases in both population spikes (Beck et al., 1985) and field excitatory postsynaptic potentials (EPSPs) (Ropert, 1988) have been observed in area CA1. Two different cellular mechanisms have been suggested to underly this excitatory action of 5-HT. First, suppression of the Ca^{2+}-activated K^+-current (I_{AHP}) will lead to increased cell firing or, second, a decrease in the voltage-dependent K^+-conductance, I_m, leads to an overall depolarization of the cell (Colino and Haliwell, 1987). These modulations may be mediated via 5-HT_4 receptors, 5-HT_{1C} receptors or by a novel, presently uncharacterized subtype (Andrade and Chaput, 1991; Beck, 1992; Chaput et al., 1990).

Effects in the Entorhinal Cortex

Although similar membrane-potential changes following 5-HT application have been reported for neurons of the entorhinal cortex and the hippocampus (Andrade and Nicoll, 1987; Colino and Haliwell, 1987; Schmitz et al., 1995; 1997; Segal, 1980; Sizer et al., 1992), the effects of serotonin on intrinsic properties of EC-neurons are less consistently observed and are less pronounced than in hippocampal neurons (Schmitz et al., 1995, 1997, 1998; Sizer et al, 1992). The mechanism underlying the hyperpolarization of neurons in the EC is likely to be the same as in CA1, where the hyperpolarization is mediated by a GTP-dependent K^+-conductance (Andrade, 1991; 1992; Andrade and Nicoll, 1987; Colino and Haliwell, 1987). Recent experiments in our laboratory revealed various lines of evidence consistent with this proposal (Schmitz et al., 1998). First, the 5-HT-induced hyperpolarization reversed at –90 mV and was blocked by both Cs^+ and by the lidocaine derivate QX314, which strongly suggests that the hyperpolarization results from the opening of K^+ channels. Second, the hyperpolarization was abolished when recorded with a patch pipet, which suggests that the effect is dependent on a soluble factor in the intracellular milieu. Third, by including GTP in the

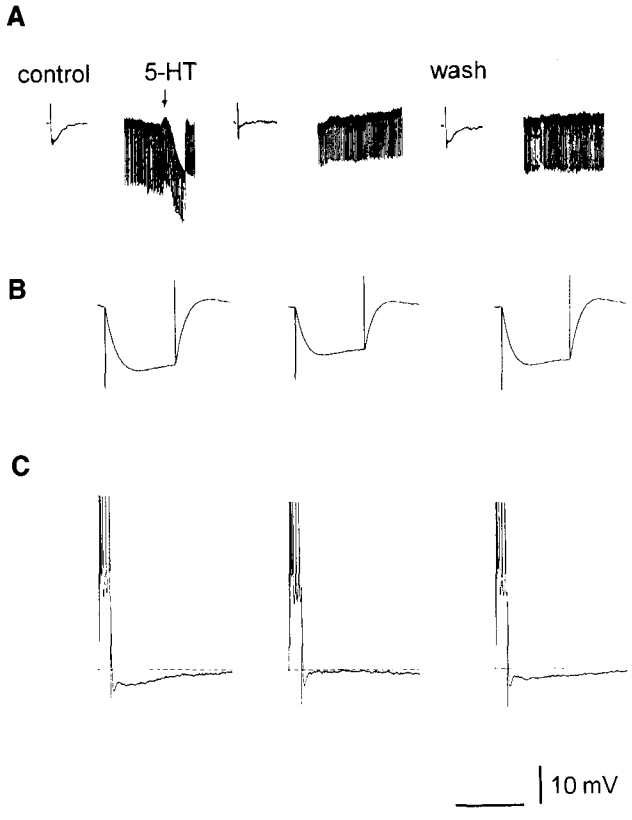

Fig. 1. Effects of 5-HT on the membranepotential **(A)**, the input resistance **(B)**, and the slow AHP (**A** and **C**) of the same CA1 pyramidal cell. In **(A)** the downward deflections represent the changes in membrane potential during negative current pulses. Application of 5-HT resulted in a large hyperpolarization that we brought back to the control potential by constant positive current injection. The 5-HT application was associated with a decrease in the input resistance as shown in **(B)**. In **(C)** (*see* also the chart recorder traces in **(A)** we show that the slow AHP was reduced following 5-HT, however the fast AHP was unchanged. Note the differences in time scales (time-bar represents 5 s and 1 min for **(A)**; 100 ms for **(B)**; 500 ms for **(C)**.

internal solution of the patch pipet, the response could be restored. Therefore, we suggest that the cellular mechanism responsible for the 5-HT-induced hyperpolarization is the same in the entorhinal cortex as in the hippocampus (Schmitz et al., 1998).

It has been previously shown that serotonin modulates oscillatory behavior of neurons in the hippocampus (Assaf and Miller, 1978; Vanderwolf, 1988). Additionally it has been reported that layer II stellate cells of the entorhinal cortex show rhythmic membrane-potential oscillations in vitro (Alonso and Klink, 1993; Alonso and Llinás 1989; Klink and Alonso, 1993). Such rhythmogenesis is functionally important for the EC-hippocampus interactions (Buzsáki et al., 1995; Chrobak and Buzsáki, 1994). It was therefore of particular interest whether 5-HT has any influence on membrane-potential oscillations in these cells. We could clearly identify entorhinal stellate cells on the basis of their electrophysiological characteristics (depolarization-induced "sag," early first action-potential) (Alonso and Klink, 1993), but we failed to find any modulatory effects of serotonin on their membrane-potential oscillations (Schmitz et al., submitted). Since we artificially induced membrane-potential oscillations by simply injecting positive current into the cell, we can not exclude a modulatory role of serotonin on oscillatory potentials in vivo, in which some of the oscillations are driven via cholinergic inputs from septal nuclei (Dickson et al., 1994). Although we can not rule out this possibility, we exclude a modulatory role of serotonin on the intrinsic ionic mechanisms for the subthreshold oscillations in EC layer II cells.

Effects of Serotonin on Synaptic Transmission

Effects in the Hippocampus

EPSP-IPSP sequences in CA1 pyramidal cells after Schaffer collateral stimulation show typical changes after the application of serotonin. Occasionally, an increased EPSP amplitude was observed (Schmitz et al., 1995a,b; Segal, 1990), but the most prominent effect of serotonin is a reduction in the polysynaptic fast and slow IPSPs (Ghadini et al., 1994; Oleskevich and Lacaille, 1992; Schmitz et al., 1995; Segal, 1990).

The effect on inhibitory transmission has been studied more precisely on monosynaptically elicited IPSPs in the absence of excitatory synaptic transmission (Davies et al., 1990) (Fig. 2.) Under these conditions the peak amplitudes of the monosynaptic fast and slow IPSPs were strongly reduced following the application of 5-HT (Schmitz et al., 1995). The reduction of the slow ($GABA_B$-receptor mediated) IPSP was larger than the reduction of the fast IPSP, although both were significantly reduced, *see* Fig. 2A.

In CA1 pyramidal cells, both types of monosynaptic IPSPs overlap in time (Davies et al., 1993), therefore the apparent decrease in the fast IPSP could arise from the larger depression of the slow IPSP. However, isolated fast IPSPs (in the presence of the new potent $GABA_B$ antagonist, CGP55485A; Davies et al., 1993) are still reduced by 5-HT. It is also important to point out that the decrease in postsynaptic PSP amplitudes does not result from the general increase in membrane conductance under 5-HT (Ginsborg, 1973). In fact, when the 5-HT-activated K^+ channels are blocked by Cs^+ or the lidocaine derivate QX314 (Andrade, 1991), serotonin still decreases the fast IPSP/Cs (Schmitz et al., 1995), *see* Fig. 2B. Different mechanisms might account for the effect of serotonin on inhibitory synaptic responses in the hippocampus. It is conceivable that postsynaptic ion channels are modulated directly or indirectly via the activation of G proteins and second-messenger pathways (Clarke et al., 1987; Kelly et al., 1991; Pennington et al., 1993). However, 5-HT has no effect on GABA-mediated potentials/currents evoked by direct application of GABA to pyramidal cells (Schmitz et al., 1995; Segal, 1990), *see* Fig. 2C. The effects of serotonin on interneurons in the hippocampus suggest a presynaptic mechanism of action. Putative inhibitory interneurons are hyperpolarized by 5-HT (Ghadimi et al., 1994; Schmitz et al., 1995; Segal, 1990) and evoked EPSPs are strongly reduced in these cells (Schmitz et al., 1995), *see* Fig. 2D. Whereas the hyperpolarization is most likely caused by the activation of an intrinsic K^+ conductance, the decrease in evoked excitatory transmission by 5-HT suggests that serotonin can reduce glutamate release from axon terminals onto the interneurons (Schmitz et al., 1995; Singer et al., 1996) or negatively modulate the postsynaptic glutamate receptors of the interneurons (Murase et al., 1990). In summary, most reported data indicate that 5-HT modulates fast and slow synaptic inhibition of principal cells by presynaptic mechanisms (Mintz et al., 1989) involving the inhibition of inhibitory interneurons (Schmitz et al., 1995; Segal, 1990).

The effects on inhibitory synaptic responses are mimicked by the $5\text{-}HT_{1A}$ receptor agonist, 8-OH-DPAT, and prevented by the $5\text{-}HT_{1A}$ receptor antagonist, NAN-190, and are therefore likely mediated via the activation of the $5\text{-}HT_{1A}$ receptor (Schmitz et al., 1995).

Effects in the Entorhinal Cortex

Experiments with serotonin in the EC revealed a dose-dependent suppression of both excitatory (Schmitz et al., 1995; 1997) and polysynaptic inhibitory postsynaptic potentials by serotonin (50% reduction at approx 1 μM) (Schmitz et al., in press). Inhibitory transmission was only affected upon polysynaptic stimulation (probably because of the depression of the excitatory transmission to interneurons). Thus, the most potent effect of serotonin in EC is a general depression of excitatory synaptic transmission. The highly potent effect on excitatory postsynaptic potentials contrasts to data from hippocampal pyramidal cells where high concentrations of 5-HT are necessary to reduce EPSPs (Jahnsen, 1980; Schmitz et al; 1995) and where lower concentrations can even transiently increase the EPSP amplitude (Schmitz et al., 1995a,b; Segal, 1990).

Several mechanisms might account for the effect of serotonin on excitatory synaptic responses in the superficial layers of the entorhinal cortex. It is conceivable that postsynaptic ion channels are modulated indirectly via the activation of G proteins and second-messenger pathways. In fact, most of the 5-HT-induced changes of neurons have been shown to be

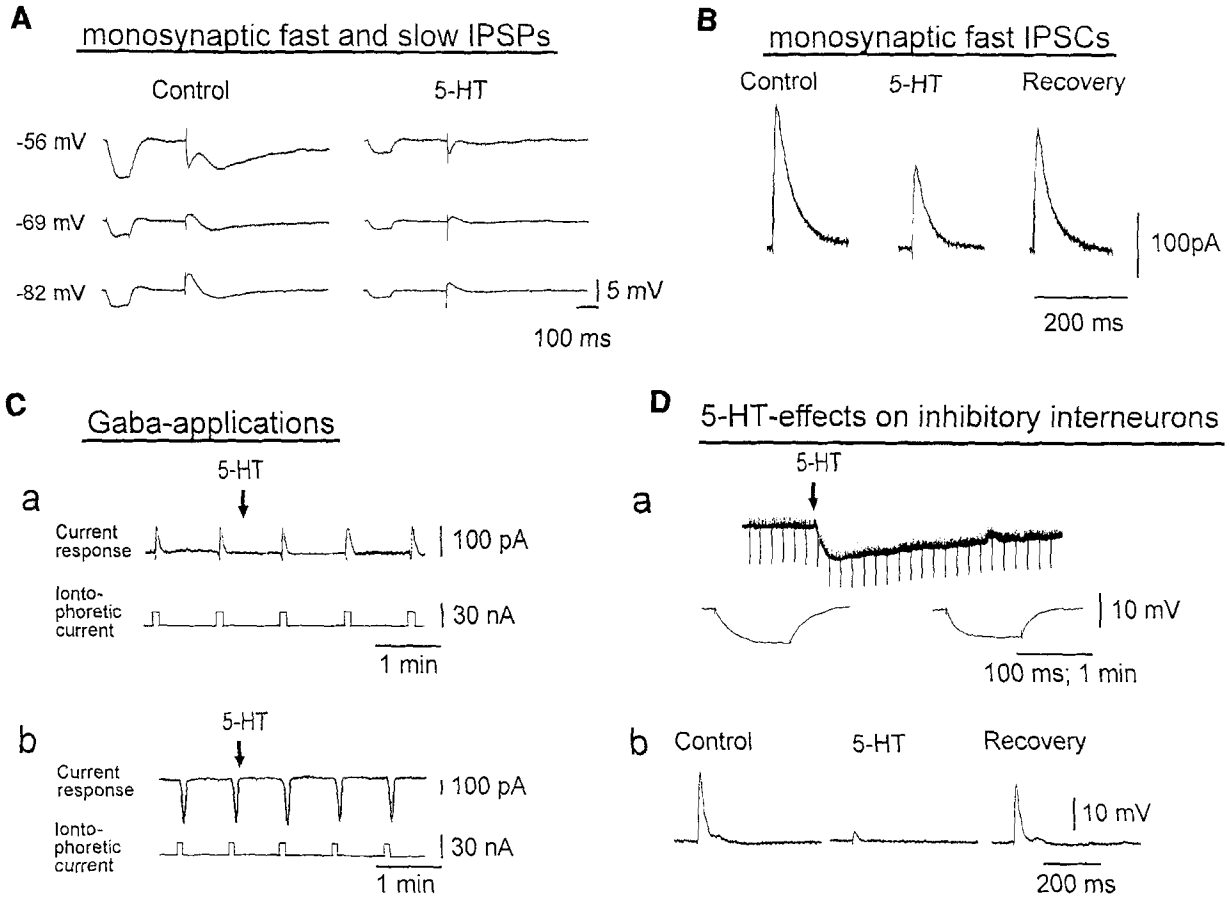

Fig. 2. **(A).** Monosynaptic IPSPs (close stimulation site in the presence of NBQX and APV) were evoked in a pyramidal cell in area CA1 of the hippocampus before and after the application of 5-HT. A 100-ms current prepulse was given prior to the evoked synaptic potential in order to monitor bridge balance and also to show the change in total membrane conductance following the application of 5-HT. Measured at their peaks and close to resting membrane potentials both fast and slow IPSPs were reduced following 5-HT application. **(B).** Isolated fast monosynaptic IPSCs (close stimulation, NBQX, and APV in the bath, Cs^+ acetate and QX314 in the electrode) were reduced following application of 5-HT. The cell was voltage clamped at −52 mV and following 5-HT application the fast IPSCs were clearly reduced in this cell. There was no change in the current required to hold the cell at −52 mV and therefore no intrinsic conductance increase that could have been responsible for the reduction of the fast IPSCs. Recovery was observed after a few minutes. **(C).** Effects of 5-HT on the responses of a pyramidal cell to iontophoretically applied GABA. *a.* When applied to the soma of the cell, GABA elicited mixed biphasic current responses. The somatic responses reversed at −73 mV, whereas the dendritic responses reversed at −49 mV. Neither of these responses were affected by 5-HT. Note also the lack of any outward current during the application of 5-HT (the cell was filled with Cs^+ acetate and QX314). *b.* Effects of 5-HT on the responses of a cell to GABA applied to its dendrites. GABA elicited an inward current response that reversed at a mean value of −47 mV. There was no change in the GABA-induced currents following the application of 5-HT by a drop application placed in the dendritic tree. The responses of the cells to the GABA applications, as well as the iontophoretic current, are shown on a slow time scale. Note the absence of any outward current following the application of 5-HT. **(D).** Responses of a putative inhibitory interneuron to 5-HT. *a.* Following the application of 5-HT to this cell, a large hyperpolarization (upper trace) was observed that was also associated with a reduced input resistance (lower trace). *b.* The response of the same cell as in *a.* to low-intensity Schaffer collateral stimulation (1.7 V). A clear EPSP was seen at this holding potential of −81 mV. The EPSPs were strongly reduced by 5-HT. Note also the presence of the spontaneous EPSPs within the averaged traces (6 sweeps). These recordings were made after a second application of 5-HT to this cell when the membrane potential during the 5-HT-induced hyperpolarization was returned to control levels by injection of constant positive current.

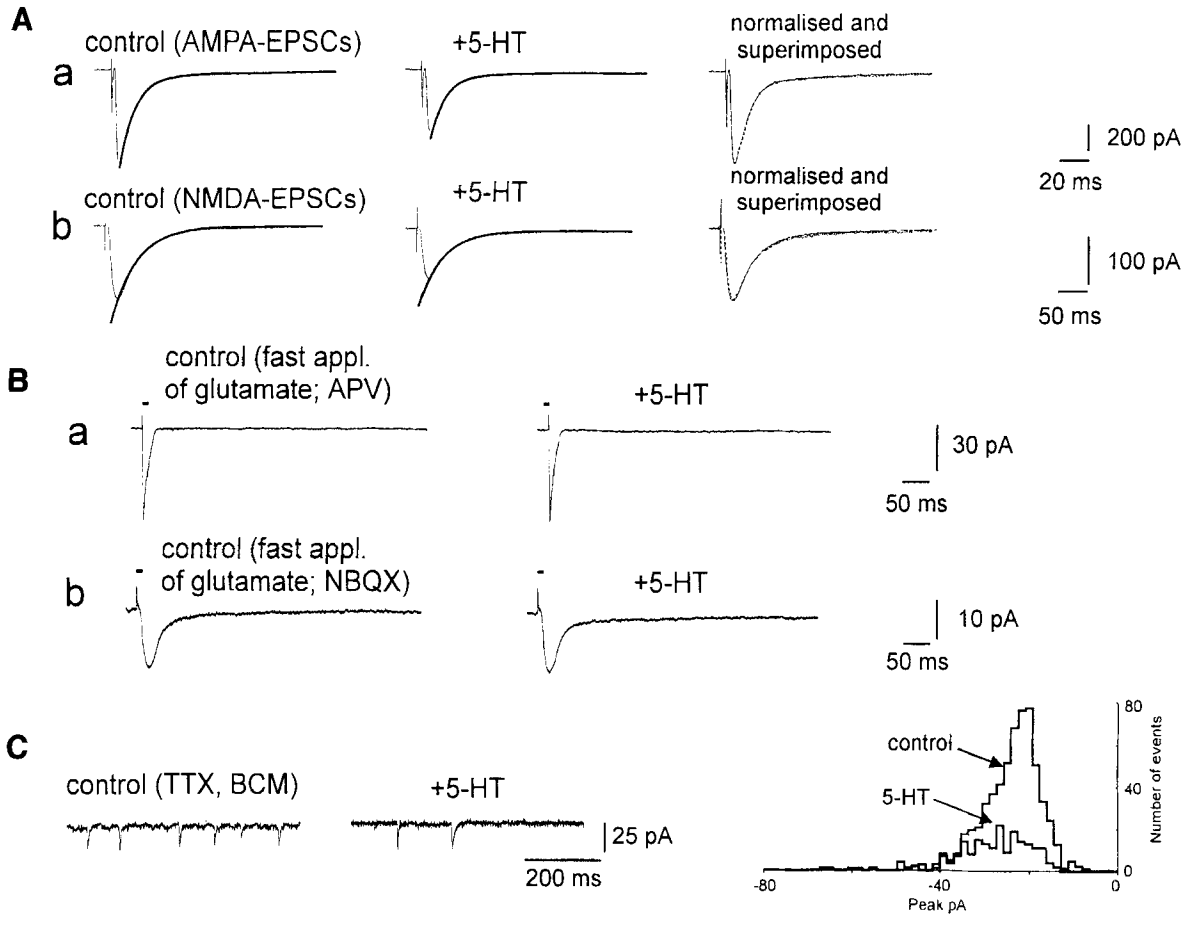

Fig.3. **(A).** Influence of serotonin on AMPA- and NMDA-receptor-mediated EPSCs in the EC. Note the different time and amplitude scales. Serotonin depressed both AMPAR- as well as NMDAR-mediated EPSCs (in APV, bicuculline) in two different projection cells of the entorhinal cortex. *Aa.* 5-HT reduced the AMPA-receptor-mediated EPSCs (in the presence of APV and bicuculline) in a layer III projection neuron of the medial entorhinal cortex. There was no outward current following the application of serotonin. *Ab.* 5-HT also reduced the NMDA-receptor-mediated EPSCs (in NBQX, bicuculline) in another projection cell of the superficial layers of the entorhinal cortex. Following the 5-HT application, no outward current was noted in this cell. Note that the kinetics of both AMPA- as well as NMDA-receptor mediated EPSCs were unchanged (*see* the normalized and superimposed responses; right traces in **[A]**). **(B).** Influence of serotonin on AMPAR- and NMDAR-mediated currents activated by fast application of glutamate to outside-out membrane patches isolated from two different pyramidal cells (identified with infrared-difference interference contrast technique) of layer III of the entorhinal cortex. *Ba.* Serotonin (50 μ*M*) had no effect on isolated AMPAR-mediated currents when elicited by a fast application of glutamate (10 m*M*) in the presence of 60 μ*M* ±APV in both barrels. *Bb.* Glutamate-activated currents in the presence of 20 μ*M* NBQX and 10 μ*M* glycine, while the external Mg^{2+} was omitted (both barrels). Again serotonin did not show any effects on the NMDAR-mediated currents. **(C).** Effects of serotonin on miniature EPSCs in a layer III projection cell of the entorhinal cortex. On the left hand side, the effects of 5-HT in original recordings are shown. The events were recorded at −60 mV in the presence of 5 μ*M* TTX and 5 μ*M* bicuculline. On the right hand side, corresponding frequency histogram of mEPSCs amplitude before and after bath application of 50 μ*M* serotonin for a short period of 5 min is shown. Serotonin clearly reduced the frequency (number of the events) of the spontaneous miniature EPSCs, whereas the mean amplitude was not significantly changed. When analyzing the amplitude distribution with a cumulative probability, a small shift to the left (bigger amplitudes) could be observed, but these changes were not significant (Kolmogorov-Smirnov test $p = 0.5$; not shown). The histograms were plotted with a bin-width of 1.6 pA and were composed of 668 events under control, 209 events with serotonin, and 418 events after wash out (not shown).

mediated mainly by a pertussis-toxin-sensitive G protein (Clarke et al., 1987; Kelly et al., 1991; Pennington et al., 1993). Such effects of serotonin can be blocked by intracellular perfusion with a patch pipet if no GTP is included (Andrade, 1992; Schmitz et al., 1998). However, the effects of serotonin on EPSP/Cs are identical in sharp microelectrode recordings and in patch-clamp experiments without GTP (Schmitz et al., 1998), *see* Fig. 3A. Therefore, a postsynaptic G-protein-mediated cellular pathway is very unlikely to underly the depression of excitation. Alternatively, serotonin might directly modulate both the AMPA- and the NMDA-receptors and thereby inhibit transmitter binding or ion flow through these ligand-gated ion channels. Indeed, it has been shown that serotonin can directly modulate NMDA-receptors in dorsal-spinal-cord neurons (Murase et al., 1990) and also in *Xenopus* oocytes injected with whole-rat-brain mRNA (Blank et al., 1996). However, serotonin had no effect on the amplitude and the kinetics of the glutamate-activated currents in isolated patches (Schmitz et al., 1998), *see* Fig. 3B. Therefore, recent data from our laboratory largely exclude any postsynaptic mechanism underlying the EPSP/Cs modulation by serotonin. It is therefore likely that the depression of synaptic excitation by 5-HT is caused by a presynaptic reduction of glutamate release from the axonal terminals, although fluorometric enzyme-assay experiments in the entorhinal cortex showed no effects of serotonin on the glutamate release (Sizer et al., 1992). In contrast, our experiments revealed that serotonin clearly reduced the frequency of miniature EPSCs without affecting the amplitude distribution (Schmitz et al., 1998), *see* Fig. 3C. Thus, it is likely that serotonin suppresses the release of glutamate from synaptic terminals by a sodium-independent process. In CA1, there is evidence that at high concentrations (≥ 100 μ*M*) serotonin can reduce excitatory synaptic transmission by blocking presynaptic Ca^{2+}-entry (Schmitz et al., 1995). Moreover, it has recently been shown that serotonin inhibits glutamatergic transmission onto rat moto neurons by a presynaptic mechanism (Singer et al., 1996) and that glutamate is coreleased by serotonergic neurons (Johnson, 1994). Additionally it has been reported that serotonin via 5-HT_3 receptors can inhibit acetylcholine release in cotical tissue (Barnes et al., 1989).

Serotonin and Epileptiform Activity

It has been reported several times that serotonin is involved in seizure generation (Meierkord, 1994; Tecott et al., 1995; Vécsei, 1993; Wada et al., 1993). However, there seems to be regional differences in its involvement in seizure activity. Whereas 5-HT blocks different patterns of low Mg^{2+}-induced epileptiform activity in the entorhinal cortex, it was ineffective in the hippocampus (Schmitz et al., 1997) (*see* Fig. 4). The mechanism to explain the anticonvulsant effects of 5-HT in entorhinal cortex seems to be a potent reduction of AMPA- and NMDA-receptor-mediated EPSP/Cs (Schmitz et al., 1995; 1997; 1998). In contrast EPSPs evoked in CA1 pyramidal cells following Schaffer collateral stimulation are slightly affected or even increased by 5-HT (Schmitz et al., 1997; 1995; Segal, 1990; Segal et al., 1989), thereby explaining the lack of any effects of 5-HT upon epileptiform activity in either CA3 or CA1. In addition, serotonin blocked the progression of the epileptiform activity in the entorhinal cortex, a mechanism that may rely on its ability to maintain the activity of the Na^+/K^+-ATPase (Schmitz et al., 1997).

Serotonin and Hippocampal-Entorhinal Cortex Physiology

Here we describe the effects of 5-HT on the modulation of inhibition of the principal output cells of the hippocampus and the selective depression of excitation in the entorhinal cortex. We are aware that studies in vitro may not accurately reflect the situation in vivo. In laboratory experiments, we can only mimic the actions of 5-HT with bath and drop applica-

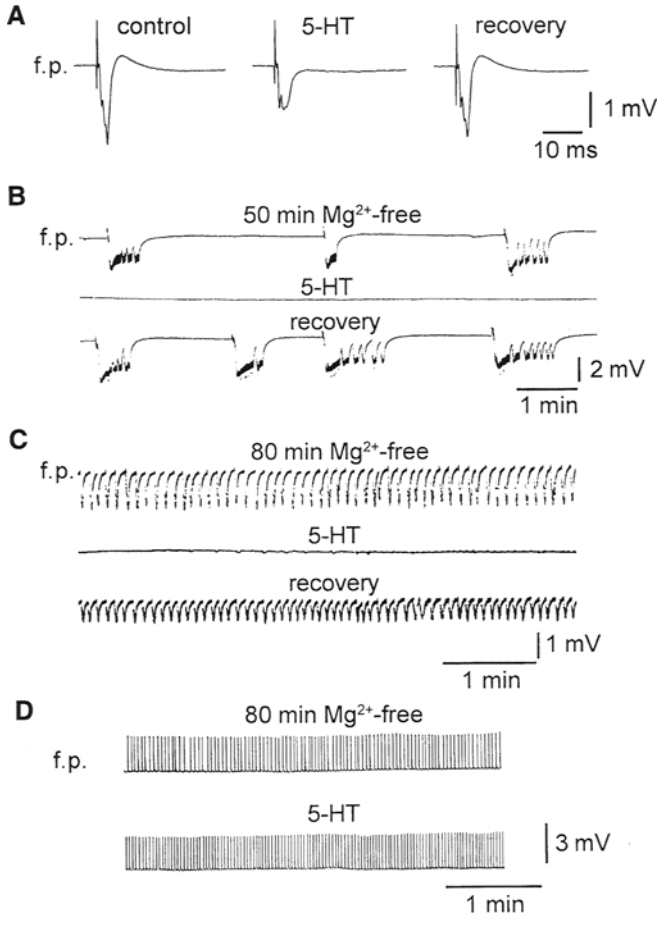

Fig.4. **(A).** Effects of serotonin on stimulus-evoked (stimulation of the lateral EC) field potential responses in layer III of the medial entorhinal cortex. Serotonin (1 μ*M*) reduced the second and third negative response as well as the late-positive component of the stimulus evoked field potentials in layer III of the entorhinal cortex, whereas the first negative response was not affected by serotonin with this concentration. **(B).** Pharmacological effects of serotonin upon the Mg^{2+}-free-induced seizure-like events recorded extracellularly from the deep layers of the entorhinal cortex. **(C).** Serotonin not only blocked the seizure-like events but also blocked late recurrent discharges in the entorhinal cortex (another slice as in **[B]**), which are known to be resistant to all clinically employed anticonvulsant drugs. **(D).** In contrast to the situation in the entorhinal cortex, serotonin was insufficient when tested in the hippocampus on short recurrent discharges even in concentrations up to 100 μ*M*.

tions whereas in vivo the release of 5-HT will depend upon the activity within the raphe nuclei. In addition, the concentrations of 5-HT used may be very different from those encountered in vivo.

In vitro results show that 5-HT can excite pyramidal cells in the hippocampus by reducing both fast and slow synaptic inhibition (Ghadimi et al., 1994; Oleskevich and Lacaille, 1992; Schmitz et al., 1995; Segal, 1990) and also via slow depolarizations and reductions in the sAHP (Andrade and Chaput, 1991; Colino and Haliwell, 1987; Schmitz et al., 1995; Segal et al., 1989; Torres et al., 1995). The only antiexcitatory effect on pyramidal cells is a membrane hyperpolarization (Andrade and Nicoll, 1987;

Colino and Haliwell, 1987; Segal, 1980). Indeed, there is anatomical evidence showing a major serotonergic innervation into stratum lacunosum moleculare (SLM) and there selective onto calbindin-positive inhibitory interneurones (Freund et al., 1990). Therefore, it seems that the known anatomy is consistent with our electrophysiological results. In contrast to the situation in the hippocampus, serotonin potently reduces synaptic excitation in all layers of the EC (Schmitz et al., 1995; 1997, 1998; Sizer et al., 1992). The changes in the EC are drastic enough to suppress extracellular field potential responses and therefore will markedly alter the output behavior of the entorhinal cortex (Schmitz et al., submitted). This will not only alter the behavior of the entorhinal cortex itself but will also influence the hippocampus. The superficial cells of the EC form the two branches of the perforant path, the main input to the hippocampus (Steward and Scoville, 1976). In vivo, 5-HT decreases feed forward inhibition of the dentate gyrus and thus increases excitability (Richter-Levin and Segal, 1990). According to our data (Schmitz et al., 1995; 1998), this might be a direct consequence of the strong depressant effects of serotonin on layer II cells of the entorhinal cortex. This will reduce the activation of inhibitory interneurons via the perforant path and aggravate the direct depressant effects of 5-HT on inhibitory interneurons, thereby increasing the excitability of granule cells (Richter-Levin and Segal, 1990). A number of different effects of serotonin on synaptic potentials in area CA1 and CA3 of the hippocampus have been reported. Increases in EPSPs (Schmitz et al., 1995a,b; Segal, 1990) and decreases in fast and slow IPSPs (Oleskevich and Lacaille, 1992; Schmitz et al., 1995a; Segal, 1990) have been observed under 5-HT. The effects of 5-HT on layer III cells of the entorhinal cortex, which predominantly activate inhibitory cells in area CA1 (Empson and Heineman, 1995a,b; Soltesz, 1995), may well contribute to the disinhibition of area CA1 thereby increasing the excitability in this region.

However, beside the functional effects of serotonin in the hippocampus and the entorhinal cortex in the adult animal, the serotonergic system is closely related to the development of the cortex. In this context, it has been reported that a serotonin excess during a critical period of development leads to a lack of the charcteristic "barrel-like clustering" of the somatosensory cortex (Cases et al., 1996).

Serotonin and Hippocampal-Entorhinal Cortex Pathophysiology

The mechanisms for population synchrony in CA1 and CA3 during low Mg^{2+}-induced epileptiform activity are a mixture of pre- and postsynaptic effects as well as of reduced charge screening (Walther et al., 1986). 5-HT is unable to block the epileptiform activity in both these regions (Schmitz et al., 1997) and also has variable effects upon Schaffer collateral-stimulated EPSPs (Jahnsen, 1980; Schmitz et al., 1995a,b; Segal, 1990). This lack of effect and the mixed excitatory and inhibitory effects of 5-HT in the hippocampus (Colino and Haliwell, 1987; Okuhara and Beck, 1994; Oleskevich and Lacaille, 1992; Schmitz et al., 1995a,b; Segal, 1980; 1990) suggest that, altogether, 5-HT cannot prevent population synchronization in CA1 or CA3.

In contrast to the situation in the hippocampus, both the seizure-like events and the late recurrent discharges in the entorhinal cortex can be blocked by serotonin (Schmitz et al., 1997). Synchronization during low Mg^{2+}-induced epileptiform activity in the entorhinal cortex most likely occurs through the large NMDA-receptor-mediated recurrent excitatory circuits between the EC cells (Dhillon and Jones, 1995; Jones, 1993; 1988). The massive reductions in the stimulus-evoked NMDA receptor-mediated EPSP/Cs of the superficial and deep layer cells suggests that serotonin most likely reduces synchronization during the epileptiform activity in this way. 5-HT-induced hyperpolarizations may also contribute to reducing synchronization.

Overall, of the diverse actions of 5-HT in the hippocampus, many are excitatory. This probably explains its inability to modify epileptiform activity in this region. In contrast, the depressing effects of 5-HT on excitatory synaptic transmission in the entorhinal cortex may explain its potent effects on both early and late forms of low Mg^{2+}-induced epileptiform activity.

An interesting observation following the application of 5-HT to seizure-like epileptiform activity in the entorhinal cortex was the subsequent prolongation of the transition into the late recurrent discharge type of activity (Schmitz et al., 1997). A reduction in $GABA_A$-ergic inhibition is thought to be responsible for this transition in the entorhinal cortex (Pfeiffer et al., 1996; Zhang, C. L. unpublished data) and also for the transition to longer bursts in area CA3 (Heinemann, 1994). The reduction in $GABA_A$-ergic inhibition in CA3 was attributed to a reduction in the ATP/ADP ratio and phosphorylation potential following the lack of Mg^{2+} from the cells (Whittington et al., 1995) and a similar mechanism may apply in the entorhinal cortex. How serotonin prevented the transitions between the two types of epileptiform activity in the entorhinal cortex is not clear. Recent data suggest that one mechanism may be its ability to restore the long lasting hyperpolarizations following seizure-like events (Schmitz et al., 1997). These events resemble hyperpolarizations following tetanic stimulation or repetitive glutamate applications to hippocampal neurons that represent the activity of the ATP-dependent Na^+/K^+ exchanger (Fukuda and Prince, 1992a,b; Gustafsson and Wigström, 1983). The gradual decrease of the hyperpolarization after each seizure-like event in our cells could result from a decreased activity of the exchanger following gradual reductions of intracellular ATP concentrations. Serotonin is known to activate the Na^+/K^+ exchanger (Hernández-R. and Condés-Lara, 1989; 1992), and this was consistent with its ability to restore the eroded late hyperpolarization. Perhaps serotonin somehow prevents the ATP depletion that occurs during long exposures of cells to low Mg^{2+}-containing solutions. The mechanisms for this are not clear but the neuroprotective effects of serotonin (Nakata et al., 1992) may relate to its ability to maintain intracellular ATP.

The seizure-like events observed in the entorhinal cortex under conditions of low Mg^{2+} bear electrographic similarities to tonic-clonic seizures in humans, whereas the late recurrent discharges seem comparable to late stages of status epilepticus (Heinemann et al., 1993). Although a number of anticonvulsant drugs have been tested on these two types of epileptiform activity, the late recurrent discharges are resistant to all conventionally employed anticonvulsants (Dreier and Heinemann, 1990; Dreier, 1991; Zhang et al., 1995) even though they can be blocked by NMDA-receptor antagonists (Zhang et al., 1994). Our observation that serotonin were capable of blocking this activity, most likely through an effective reduction of NMDA-receptor-mediated excitation in the deep layers of the entorhinal cortex, was therefore consistent with the known pharmacology. Our results suggest a promising potential of serotonin-receptor agonists or serotonin-reuptake inhibitors as anticonvulsant drugs. This idea is further supported by the existence of forms of epilepsy that involve the serotonergic system, like juvenile myoclonic epilepsy, which can occur in strict relationship to the sleep-wakefulness cycle (Meierkord, 1994), that is regulated in part by serotonin (Wauquier and Dugovic, 1990). Moreover, mice lacking $5\text{-}HT_{2C}$-receptors are prone to sudden death from seizures (Tecott et al., 1995).

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