Exp Brain Res
DOI 10.1007/s00221-013-3594-1

Research Article

High dose of 8-OH-DPAT decreases maximal dentate gyrus activation and facilitates granular cell plasticity in vivo

Gergely Orban · Massimo Pierucci · Arcangelo Benigno · Mauro Pessia · Salvatore Galati · Mario Valentino · Richard Muscat · Giuseppe Di Giovanni

Received: 30 April 2013 / Accepted: 17 May 2013

Abstract Although several studies have emphasized a crucial role for the serotonergic system in the control of hippocampal excitability, the role of serotonin (5-HT) and its receptors in normal and pathologic conditions, such as temporal lobe epilepsy (TLE), is still unclear. The present study was therefore designed firstly to investigate the acute effect of 8-OH-DPAT, a mixed 5-$HT_{1A/7}$ receptor agonist, at a high dose (1 mg/kg, i.p.) known to have antiepileptic properties, in a model of acute partial epilepsy in rats. For this purpose, a maximal dentate activation (MDA) protocol was used to measure electrographic seizure onset and duration. In addition, the effect of 8-OH-DPAT on in vivo dentate gyrus cell reactivity and short- and long-term plasticity was studied. Rats injected with 8-OH-DPAT exhibited a significant reduction in MDA and epileptic discharges, a decrease in paired-pulse facilitation and an increase in long-term potentiation. This study suggests that 8-OH-DPAT or in general 5-$HT_{1A/7}$ agonists might be useful for the treatment of TLE and also have some beneficial effects on the comorbid cognitive disorders seen in epileptic patients.

Keywords Temporal lobe epilepsy · Dentate gyrus · Serotonin receptors · Memory · Depression · Serotonergic$_{1A}$ drugs

G. Orban (✉) · A. Benigno
Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, Sezione di Fisiologia Umana, "G. Pagano", Università degli Studi di Palermo, Palermo, Italy
e-mail: gergely.orban@unipa.it

G. Orban · M. Pierucci · M. Pessia · G. Di Giovanni
Istituto Euro-Mediterraneo di Scienza e Tecnologia (IEMEST), Palermo, Palermo, Italy

M. Pierucci · M. Valentino · R. Muscat · G. Di Giovanni (✉)
Department of Physiology and Biochemistry, Faculty of Medicine and Surgery, University of Malta, Msida, Malta
e-mail: giuseppe.digiovanni@um.edu.mt

M. Pessia
Department of Internal Medicine, Section of Human Physiology, University of Perugia, Perugia, Italy

S. Galati
Neurology Department, Neurocenter (EOC) of Southern Switzerland, Ospedale Civico, Lugano, Switzerland

G. Di Giovanni
School of Biosciences, Cardiff University, Cardiff, UK

Introduction

Alterations in serotonin (5-HT) neurochemistry have been implicated in the aetiology of all major cerebral disorders, ranging from schizophrenia to mood and anxiety-spectrum disorders including epilepsy (Di Giovanni et al. 2008; Bombardi and Di Giovanni 2013; Bortolato et al. 2013). Moreover, a dysfunctional serotonergic system might be responsible for the occurrence of concomitant diseases such as temporal lobe epilepsy (TLE) and comorbid depression and cognitive impairments and depression (Kanner and Balabanov 2002; Garcia 2012; Theodore et al. 2012). Among the different 5-HT receptor (R) subtypes, compelling pre-clinical and human studies have indicated an impairment of 5-HT_{1A} signal in TLE and comorbid psychiatric disorders seen in these patients (Theodore et al. 2012). Indeed, recent imaging studies have shown a reduced serotonin 5-HT_{1A}R binding in the temporal cortex and hippocampus of TLE patients (Giovacchini et al. 2005). Nonetheless, the 5-HT_{1A} system is complex, and the effects of its activation are far from

Published online: 19 June 2013

being completely characterized; moreover, the experimental results hitherto obtained are controversial. The picture is complicated further as central 5-HT_{1A}Rs are both autoreceptors in 5-HT nuclei and post-synaptic receptors in terminal field areas (Pazos and Palacios 1985), with different functional and regulatory characteristics, depending on the structures innervated (Jolas et al. 1995). Serotonergic projections to the hippocampus arise from the dorsal and median raphe nucleus (DRN and MRN), and preferentially innervate GABAergic interneurons although they are present also on principal cells (Freund et al. 1990; Freund 1992). Earlier in vivo studies reported that 5-HT releasers facilitate the response of dentate granule (DG) cells to perforant path (PP) stimulation (Richter-Levin and Segal 1990), an effect that is thought to be mediated by hippocampal post-synaptic 5-HT_{1A}Rs (Levkovitz and Segal 1997) on GABAergic interneurons and consequent inhibition of GABA release (Freund et al. 1990; Freund 1992; Gulyas et al. 1999). Consistently, 5-HT_{1A}Rs in the DG exert an excitatory effect that plays a permissive role in long-term potentiation (LTP) induction, particularly in environments with a high degree of novelty (Sanberg et al. 2006). Opposite results on DG excitability have been obtained with systemic administration of low doses of (+)-8-hydroxy-2-(di-*N*-propylamino) tetralin (8-OH-DPAT) (Klancnik et al. 1989; Sanberg et al. 2006), a mixed 5-$HT_{1A/7}$ agonist, likely due to the preferential activation of the somatodendritic 5-HT_{1A}Rs in the raphe versus the post-synaptic 5-HT_{1A}Rs that would result in hippocampal 5-HT release decrease (Sharp and Hjorth 1990; Lacivita et al. 2008). Nevertheless, the involvement of 5-HT_7Rs in PP-DG synapse cannot be ruled out, considering new evidence of their involvement in CA3-CA1 hippocampal plasticity (Costa et al. 2012a, b). As far the 8-OH-DPAT anticonvulsant effect is concerned, it is noteworthy that only high doses of the drug are effective in various TLE experimental models, such as in vivo and in vitro hippocampal seizure models (Theodore 2003; Lopez-Meraz et al. 2005) and kainic acid (KA)- and pentylenetetrazol (PTZ)-induced status epilepticus (SE) (Lopez-Meraz et al. 2005, 2007). Scanty results exist instead of the effect of 8-OH-DPAT on DG hyperexcitability, for instance, in the DG kindling model, systemic activation of 5-HT_{1A} produced no epileptic effect (Cagnotto et al. 1998; Watanabe et al. 1998). Therefore, there is enough evidence to suggest the use of 5-HT_{1A} agonists for the treatment of TLE. Noticeably, the effect of the anticonvulsant high dose of 5-HT_{1A} agonists on the synaptic plasticity of hippocampal cells under normal conditions has not yet been investigated. This evidence is very important in the light of the comorbid cognitive impairment seen in epileptic patients and the deleterious effects of conventional antiepileptic drugs (AEDs) on memory (Motamedi and Meador 2004).

With the aim of filling this gap, we performed the present in vivo electrophysiological studies to evaluate the effects of the systemic administration of a high dose of 8-OH-DPAT (1 mg/kg, i.p.) on the reactivity of dorsal hippocampal granular cells under hyper- and normal excitable conditions following PP stimulating paradigms in urethane anesthetized rat. To this end, we used two different tetanic high-frequency stimulation (HFS) protocols to induce either the phenomenon of maximal dentate activation (MDA, 20 Hz), a model of partial complex (limbic) seizures, or long-term potentiation (LTP, 200 Hz) at PP-DG synapses. Single or paired-pulse stimulations delivered to PP fibres were instead used (1) to evaluate dentate evoked field potential (i.e. the field excitatory post-synaptic potential (fEPSP) slope and population spike (pSpike) amplitude), (2) to produce input/output curves (100–1,000 μA) and (3) to compute the paired-pulse index (PPI) for paired-pulse stimulation ranging from 20 to 600 ms. Our results by supporting previous work further suggest that 5-HT_{1A}Rs are potential therapeutic targets for the treatment of TLE seizures and also show a potential benefit for the comorbid cognitive impairment seen in patients with this form of epilepsy.

Methods and methods

Surgical procedures

The care and treatment of all animals conformed to Council Directive 86/609/EEC and with the Animals Scientific Procedures Act 1986, and local regulations for the care and use of animals in research. All efforts were taken to minimize the animals' pain and suffering and to reduce the number of animals used.

Experiments were conducted on male Sprague–Dawley rats weighing ~300 g from Charles River Laboratories UK, which were anesthetized by i.p. urethane (Sigma-Aldrich Co., Milano, Italy) (1.2 g/kg) administration and positioned in a David Kopf stereotaxic frame. Body temperature was maintained by a heating pad and a temperature controller unit (Temperature Control Unit HB 101/2, Letica Scientific Instruments).

Field potentials were evoked by stimulating the PP (AP: −8.3 L: 4.8 V: 3.4) (Paxinos and Watson 1986) with a bipolar stimulating electrode (bifilar twisted stainless steel, Stainless Steel Wire AISI316, Advent). The recording electrode (Tungsten Low Resistance Electrode, A-M Systems Inc., Carlsborg USA) was implanted into the hilus of the DG of the hippocampus (AP: −4.8 L: 2.2 V: 3.6) (Paxinos and Watson 1986). During the surgical procedure, electrodes were advanced slowly downward until reaching the optimal depth to record PSs. In order to record

during implantation and experiment, a NeuroLog amplifier (Digitimer Ltd, high pass: 0.2 Hz, low pass: 5,000 Hz, gain: 200) was used. Using a constant current stimulator (Digitimer Ltd, model DS3), digitally controlled stimulator, square-wave pulses of 0.2 ms duration were applied, 1 per minute. Stimulus intensity was set to evoke 60–70 % of the maximum amplitude of the pSpike. After the optimal depth to record pSpike had been reached, control data were acquired after a 30 min delay to allow the tissue to recover from any trauma due to electrode implantation. The same recording and stimulation procedure were used as under implantation.

Recording of pSpike was performed using the same settings as during implantation (see above). Responses were digitized by a CED 1401 plus analogue–digital converter (Cambridge Electronic Design Ltd., Cambridge, UK), stored on a computer and averaged offline using Signal 1.9 software. Sampling rate was set to 10 kHz. Location of the recording electrode was verified histologically.

Maximal dentate activation experiments

Maximal dentate activation (MDA) was characterized electrophysiologically by (1) the onset of large-amplitude pSpikes (i.e. 20–40 mV) fired in bursts and (2) a rapid negative DC shift in baseline of DG electrical recordings (Stringer et al. 1989). Stimulus trains of 10 s (pulses of 0.3 ms duration, at 20 Hz) were delivered through the PP electrode at an initial intensity of 200 μA. If MDA was not elicited, the stimulus intensity was increased in 50 μA steps and redelivered every 2.5 min until MDA was induced. Usually, threshold was reached at 350 ± 100 μA, and then stimulus intensity was further increased by 100 μA. For each stimulus, the duration of MDA, time to onset and AD were measured as shown in Fig. 1a.

Time to onset and duration of MDA were measured as repeated seizure-inducing trains were delivered every 10 min for the next 4 h (total of 24 stimulus trains). As shown in Fig. 1a, the latency to MDA onset was measured from stimulus onset to the point of pSpike appearance with half of the maximal amplitude.

After the AD had begun to lengthen, either drug or vehicle was administered just after the fifth stimulus train. In the absence of drug, the duration of maximal dentate activation will increase and the time to onset will gradually decrease (Stringer and Lothman 1990a). In order to make comparisons across animals, the measured durations of MDA and time to onset were 'normalized' by subtracting their duration in response to the first stimulus from the duration in response to each subsequent stimulus train. Thus, for individual stimulus trains after the first, a change in duration (or time to onset) was calculated. In this way, data from separate animals were averaged and comparisons across groups of animals were made (Stringer and Lothman 1990a).

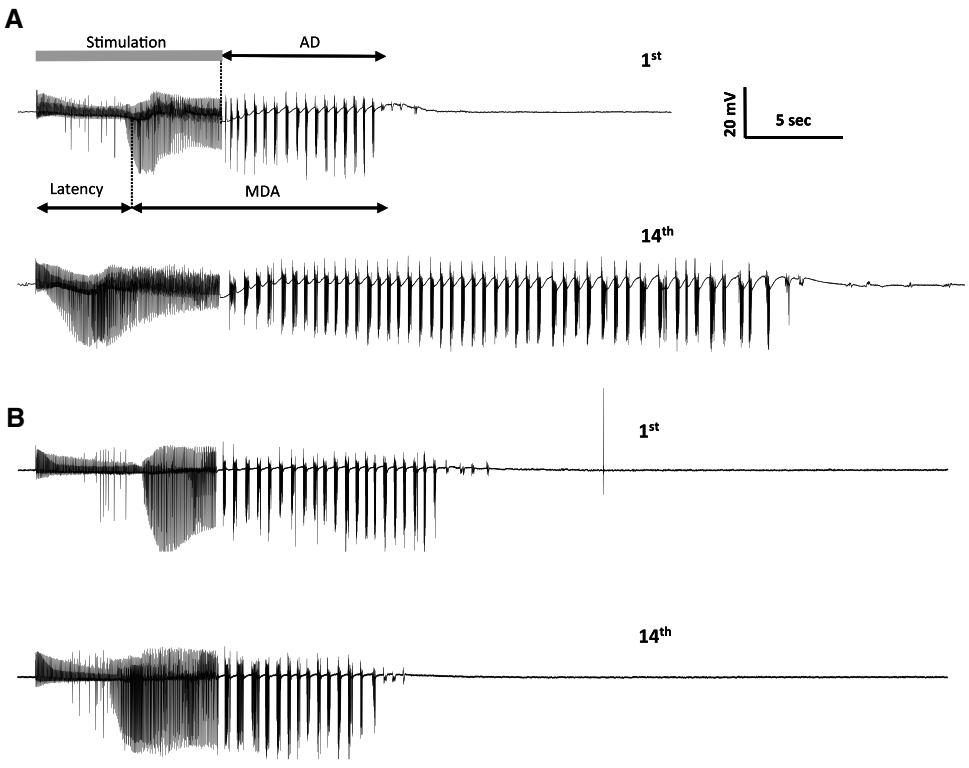

Fig. 1 Effect of 8-OH-DPAT on MDA and after discharge (AD) duration recorded in AC mode. **a** MDA is not prolonged in 8-OH-DPAT (1 mg/kg; $n = 5$) treated animals as compared with saline control rats ($n = 9$) after 14 repetitive seizure-inducing stimuli (**b**)

Time course of the drugs

After the 30 min recovery (as mentioned above), a 60 min baseline was recorded for each experiment. 5 sweeps of each different interval were averaged. A 30 s gap was kept between the sweeps. The average of these sweeps served as the control pSpike and fEPSP, and their amplitude and slope were expressed as a percentage of these control values. Following the baseline recording, drug was administered, and its effect recorded for 120 min.

I/O recordings

The recordings were started after the post-surgical recovery period when single pulses were applied with different pulse strengths (100–1,000 μA in 100 μA steps). 5 sweeps of each different pulse strength were averaged. A 30 s gap was maintained between the sweeps. Results were evaluated by plotting pSpike amplitude and fEPSP slope against the stimulus strength, and also by plotting amplitude against the fEPSP slope (I/O curves). These curves were repeated 30 min after the 8-OH-DPAT systemic injection (treatment curves) and compared with those obtained in the pre-drug period.

Paired-pulse recordings

In these experiments after the recovery, pairs of identical pulses were applied with different interpulse intervals (IPI) (20, 25, 40, 110, 150, 600 ms). 5 sweeps of each different interval were averaged. A 30 s gap was maintained between the sweeps. The paired-pulse ratio (PPR) of the pSpike amplitudes of the 1st (conditioning pulse) and 2nd (test pulse) responses was assessed in control (pre-drug) and treatment (post drug) conditions. Since the time course of the drug effects showed a peak effect reached 30 min after administration, the effect of 8-OH-DPAT was evaluated 30 min after its administration.

LTP recordings

After 30 min of post-surgical recovery, single pulses were applied. 1 pulse was applied every 60 s, and 5 responses were averaged. Pulse strength was set to evoke 30 % of the maximum pSpike amplitude. After a 10 min baseline, either vehicle or 8-OH-DPAT was administered i.p. The effect of the treatments on the baseline was observed for 30 min, and then a high-frequency pulse train (HFS) was applied (same pulse parameters as in baseline, 10 trains of 15 pulses at 200 Hz, with 1 s delay between trains) to evoke LTP.

Statistical analysis

Evaluation of the recorded data was conducted using Spike2 software (CED, Cambridge, UK). One-way analysis of variance (ANOVA) for repeated measures followed by Fisher's PLSD post hoc test was used. Differences were considered significant at $p < 0.05$.

Results

Effect of 8-OH-DPAT on the parameters of maximal dentate activation

The effect of administration of the vehicle (saline) on the time to onset and duration of MDA was determined in nine animals. There was an increase in the change of duration of MDA over the first 14 stimuli (Figs. 1, 2), and it then became quite variable reaching 24.5 ± 2.4 s after the 24th stimulus (Fig. 2a). There was also a gradual decrease in the time to onset to −2.2 ± 0.3 (at the 8th stimulus) and then a plateau (Fig. 2b). The typical effect of 8-OH-DPAT (1 mg/kg, i.p.; $n = 5$) treatment on the MDA is shown on the sample traces of Fig. 1. The increase in the duration of the MDA (Fig. 2a) was significantly blocked by 8-OH-DPAT 20 min after its systemic administration (8-OH-DPAT vs. vehicle, 8.6 ± 0.9 vs. 3.6 ± 1.5; $F_{1,12} = 7.893$, $p < 0.05$) for the entire duration of the experiment, reaching the maximum effect at the 19th stimulation (8-OH-DPAT vs. vehicle 13.6 ± 5.0 vs. 1.1 ± 2.6). The effect of 8-OH-DPAT on the change in AD followed a similar pattern to the effect of the drug on MDA elongation (not shown). On the other hand, the latency of the onset of MDA (Fig. 1b) was not affected by the 8-OH-DPAT treatment, although a not significant decrease was seen 30 min after the drug injection (8-OH-DPAT vs. vehicle: −1.5 ± 0.6 vs. −2.2 ± 0.3; $F_{1,12} = 0.087$, $p = 0.77$).

Time course

Systemic administration of 8-OH-DPAT (1 mg/kg, i.p.; $n = 3$) produced a significant increase in both the slope of the fEPSP and the amplitude of the pSpikes which attained a maximum of 121.1 ± 1.8 % (8-OH-DPAT vs. vehicle; $F_{1,6} = 17.685$, $p < 0.01$) and 121.5 ± 3.0 % (8-OH-DPAT vs. vehicle; $F_{1,6} = 5.456$, $p < 0.05$) of baseline values (Fig. 3a, b), respectively, when compared with the vehicle group (saline, $n = 5$). These effects appeared after 10 min and remained significant for the entire duration of the recording for the slope of fEPSP and in different time points for pSpike amplitude (Fig. 3a, b).

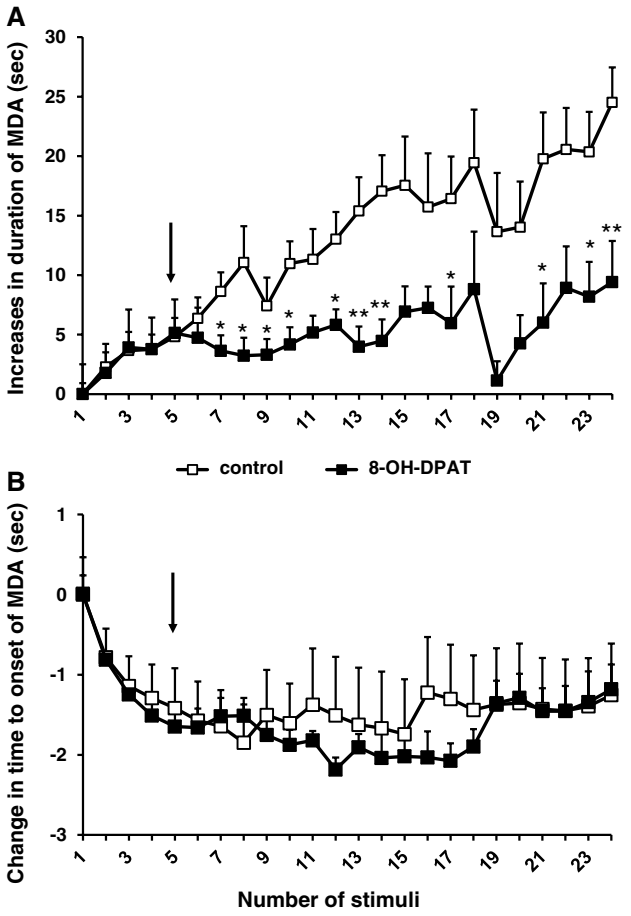

Fig. 2 Effect of 8-OH-DPAT on the parameters of MDA. The duration and time to onset of MDA were measured for each stimulus train. These values were then normalized, averaged and *plotted* (±SEM) against stimulus number. 8-OH-DPAT was administered i.p. at the *arrow*. The *open squares line* indicates the mean values from the vehicle control animals. **a** The effect of 8-OH-DPAT at 1 mg/kg ($n = 5$, *filled squares*) and vehicle ($n = 9$, *empty squares*) on the change in duration of MDA. **b** The effect of 8-OH-DPAT at 1 mg/kg ($n = 5$, *filled squares*) and vehicle ($n = 9$, *empty squares*) on the change in the time to onset of MDA. One-way ANOVA for repeated measures followed by Fisher's PLSD post hoc test; 8-OH-DPAT versus vehicle group, $*p < 0.05$, $**p < 0.01$

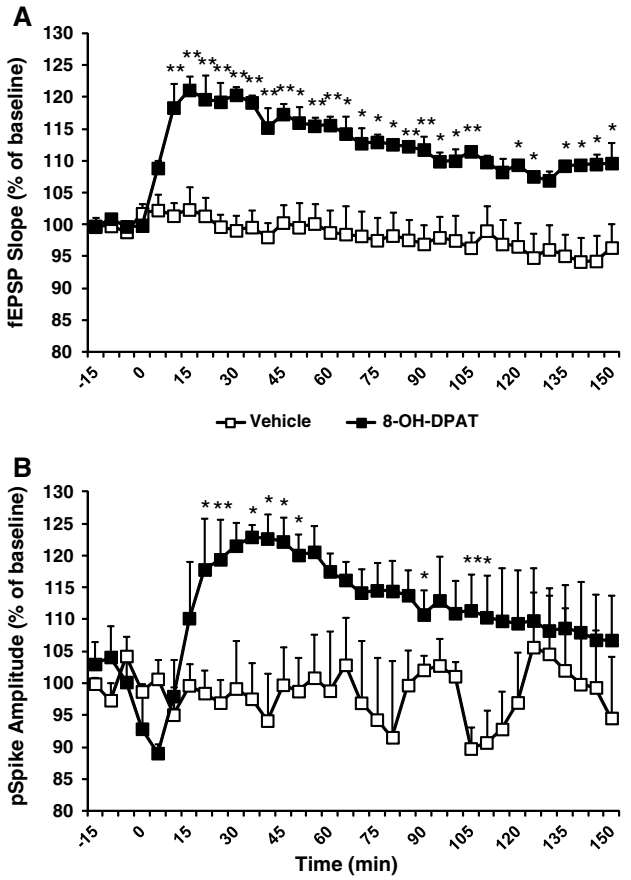

Fig. 3 Effects of peripheral administration of 8-OH-DPAT on pSpike response of dentate granular cells to perforant path stimulation. *Empty squares* saline ($n = 5$); *filled squares* 8-OH-DPAT (1 mg/kg, i.p; $n = 3$). Drugs were injected i.p. at time = 0. *Each point* the mean ± SEM of the respond, as a percentage of baseline values. In **a** the 8-OH-DPAT sustained and significant increase effect on fEPSP slope and in **b** on pSpike amplitude versus the vehicle group. One-way ANOVA for repeated measures followed by Fisher's PLSD post hoc test; 8-OH-DPAT versus vehicle group, $*p < 0.05$, $**p < 0.01$

I/O experiments

In these experiments, the stimulus strength was changed in 100 μA steps starting from 100 μA. A series of sample traces is shown in control condition and after 8-OH-DPAT treatment (Fig. 4a). To evaluate how the input/output relation of the DG cells is affected by the drug, the amplitude of pSpike and the slope of the fEPSP were plotted against each stimulus strength (Fig. 4b). No statistically significant changes were observed (8-OH-DPAT vs. control; pSpikes $F_{1,13} = 0.617$, $p = 0.45$; slope fEPSP, $F_{1,13} = 0.118$, $p = 0.74$; $n = 5$), although 8-OH-DPAT affected the pSpike amplitudes more (decreasing it) than fEPSP slopes.

Paired-pulse experiments

Pairs of pulses with identical pulse parameters were applied to the PP with different IPIs. The intervals were the following: 20, 25, 40, 110, 150 and 600 ms. In control conditions (pre-drug), the pulse intervals of 20 and 25 ms length caused a decrease in the second response (early inhibition), the 40, 110 and 150 ms intervals caused facilitation of the responses, while the 600 ms delay caused a decrease in the second response (late inhibition).

Sample traces for control and 8-OH-DPAT are shown at 3 different interpulse intervals (Fig. 5 insets). The PPR between the pSpike amplitudes of the first and second response is plotted against IPIs in control and after 8-OH-DPAT administration in Fig. 5. The inhibitory interactions were not altered by the 8-OH-DPAT treatment, while

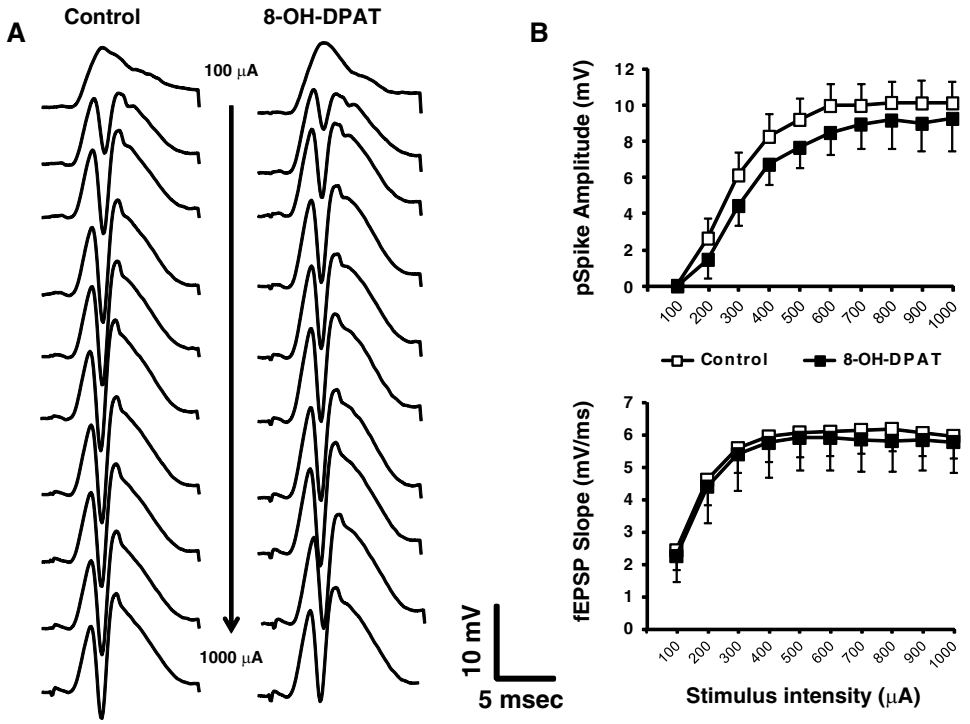

Fig. 4 Effects of peripheral administration of 8-OH-DPAT on pSpike response of dentate granular cells to perforant path stimulation with increasing stimulation strength. Input–output (I/O) responses were obtained by assessing the amplitude of the pSpike to stimulation intensities of 100 through 1,000 μA. **a** *Cartoon* showing pSpikes for pre-drug condition (control) and after administration of 8-OH-DPAT to stimulation intensities. **b** *Input–output plots* revealed a non-significant decrease in pSpike amplitude and no change of fEPSP slope produced by 8-OH-DPAT ($n = 5$; 1 mg/kg, i.p.) versus control values as the stimulation strengths were increased. Stimuli of 100–1,000 μA (0.1-ms duration) consistently evoked pSpikes that were 60–80 % of plateau responses

facilitation at 40 and 110 ms was significantly affected by the drug (8-OH-DPAT vs. control, one-way ANOVA for repeated measures, interaction treatment x stimulus interval, $F_{5,35} = 5.879$, $p < 0.01$; $n = 5$).

LTP

The 8-OH-DPAT administration significantly increased both the amplitude of the pSpike (123.9 ± 8.1 % after 25 min, 8-OH-DPAT vs. vehicle, $F_{1,7} = 10.874$, $p < 0.05$; $n = 5$) and the slope of the fEPSP (122.3 ± 3.1 % after 20 min, 8-OH-DPAT vs. vehicle $F_{1,7} = 193.707$, $p < 0.01$; $n = 5$) compared to the vehicle group ($n = 5$) (Fig. 6), similarly to the results that we obtained in the time courses experiments. According to well-established findings (Bliss and Lomo 1973), HFS induced LTP for fEPSP slope and pSpike amplitude of the vehicle group, these changes were followed up to 120 min (Fig. 6b, c). To evaluate the effect of 8-OH-DPAT treatment on the LTP without confounding effects, we subtracted the drug pre-stimulation value from the post-tetanic ones and we still observed a significant increase in fEPSP slope (8-OH-DPAT vs. vehicle, $F_{1,8} = 7.207$, $p < 0.05$) but not in the pSpike amplitudes ($F_{1,8} = 0.467$, $p = 0.51$) when they were compared to the vehicle group (Fig. 6b, c).

Discussion

To our knowledge, the present electrophysiological study is the first in vivo investigation of the effects of acute treatment of 8-OH-DPAT, at a dose (1 mg/kg, i.p.) that has been shown to have an anticonvulsant effect (Salgado and Alkadhi 1995; Gariboldi et al. 1996; Salgado-Commissariat and Alkadhi 1997; Tokarski et al. 2002; Lopez-Meraz et al. 2005, 2007), on granular cell reactivity and short- and long-term plasticity.

We used 8-OH-DPAT as it is a potent 5-HT_{1A}R agonist that has been widely used to study the function of this 5-HTR subtype (Lacivita et al. 2008) although it has been shown to act as a 5-HT_7R agonist as well (Lovenberg et al. 1993). The DG was chosen as it plays an important role in hippocampal excitability, epileptogenesis, memory processing and depression [see for recent reviews the volume edited by (Scharfman 2007)]. Indeed, the DG is commonly considered to be a gate that prevents excessive activity from entering other hippocampal regions (Heinemann et al. 1992). The breakdown of this gate, with activation of DG cells, could be a critical event in the development of seizure activity within the temporal lobe (Collins et al. 1983; Heinemann et al. 1992). Support for this idea in vivo has come primarily from studies of acutely induced seizures by PP stimulation in which maximal activation of the DG occurs and the rate of increase in its duration has been described as a paradigm analogous to electrical kindling (Stringer et al. 1989; Stringer and Sowell 1994). Although this animal model has been extensively used to screen compounds for activity against limbic seizures (Stringer and Lothman 1990a) or neuromodulators (Stringer and Erden 1995) or more recently for the effect of ketogenic diet (Bough et al. 2003), the antiepileptogenic

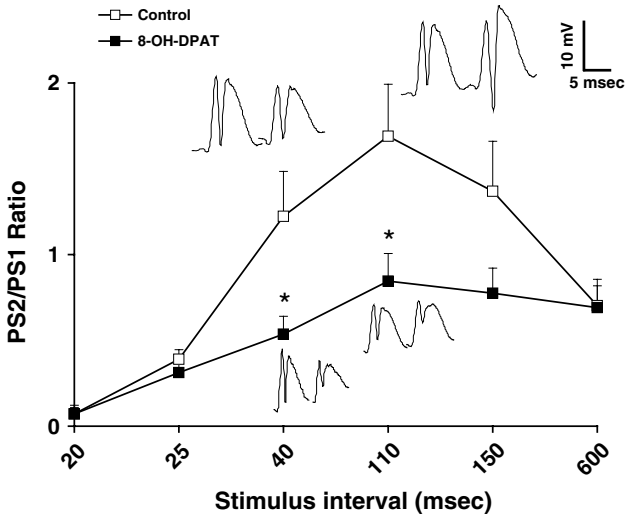

Fig. 5 Effects of peripheral administration of 8-OH-DPAT on paired-pulse relationship in the dentate gyrus. The responses in the dentate gyrus after paired stimulations 20, 25, 40, 110, 150 and 600 ms apart are shown for the pre-drug condition (control) and after administration of 1 mg/kg 8-OH-DPAT. The ratio of the amplitude of the pSpike in response to the second stimulus (PS2) is divided by the amplitude of the pSpike in response to the first stimulus (PS1) to give an inhibition ratio. If the ratio is 1, this indicates that there is no inhibition and the two pSpikes have the same amplitude. Ratios less than one indicate some degree of inhibition of the second pSpike. On the other hand, ratios more than one indicate facilitation of the second pSpike. The *graph* represents the mean ($n = 5$, ±SEM) ratios at each interpulse interval before (control) and after administration of 1 mg/kg, i.p. of 8-OH-DPAT. After administration of 8-OH-DPAT the response to the second stimulus at the 40 and 110 ms interpulse interval is about 50 % of the response to the first stimulus, indicating a loss of facilitation (sample field potentials in control and 8-OH-DPAT). One-way ANOVA for repeated measures followed by Fisher's PLSD post hoc test; 8-OH-DPAT versus control group, $*p < 0.05$

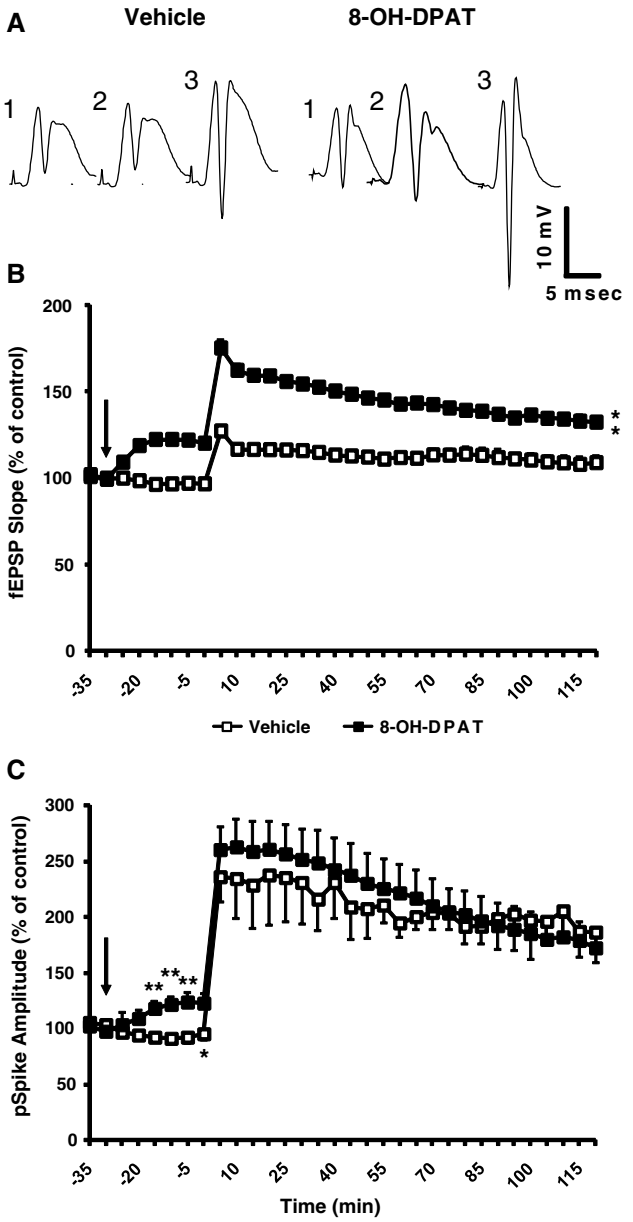

Fig. 6 Changes in LTP after 8-OH-DPAT in the perforant path-dentate gyrus synapses. **a** Sample field potentials in vehicle ($n = 5$) and 8-OH-DPAT ($n = 5$) treated rats at the baseline (*1*), after drug treatment (*2*) and HSF (*3*) time. **b** Time course changes of the slope of fEPSP before and after HSF-induce LTP in the 8-OH-DPAT and vehicle group. **c** Time course changes of the amplitude of pSpike before and after HSF-induce LTP in the 8-OH-DPAT and vehicle group. Drugs were injected i.p. at the *arrow*. One-way ANOVA for repeated measures followed by Fisher's PLSD post hoc test; 8-OH-DPAT versus vehicle group, $*p < 0.05$, $**p < 0.01$

and anticonvulsant role of 5-HT and/or its receptors subtypes has not been investigated yet. The only available electrophysiological studies of 8-OH-DPAT on DG hyperexcitability have been performed in kindled rats in chronic conditions (Cagnotto et al. 1998; Watanabe et al. 1998), both indicating a lack of effect of 8-OH-DPAT on kindling progression (Cagnotto et al. 1998) and on any other seizure parameters (Watanabe et al. 1998). Therefore, these data suggest that 5-HT_{1A}Rs may be involved in the fine modulation of hippocampal excitability, acting in concert with other neurotransmitter systems, and their activation alone may not be sufficient to interfere with the epileptogenic process in rats. Nevertheless, a lasting and selective increase in 5-HT_{1A}R density induced by kindling has been shown in rats, likely due to an adaptive response of granule cells to recurrent epileptic activity that might contribute to modulation of DG hyperexcitability (Cagnotto et al. 1998).

Opposite results have been obtained in cats, where 8-OH-DPAT increases the AD threshold, reduces the duration of partial seizures and avoids generalized seizures induced by hippocampal kindling (Wada et al. 1992, 1993). In agreement with this evidence, activation of 5-HT_{1A}Rs reduces the EEG hippocampal epileptiform activity when induced in vitro (Salgado and Alkadhi 1995;

Salgado-Commissariat and Alkadhi 1997) and in vivo by different pharmacological models of TLE (Gariboldi et al. 1996; Lopez-Meraz et al. 2005, 2007). Moreover, the administration of WAY100635, a 5-HT_{1A} antagonist, avoided the protective effect induced by the intrahippocampal infusion of serotonin on the development of pilocarpine-induced seizures (Clinckers et al. 2004). Therefore, these conflicting experimental evidence does not strongly support a potential therapeutic role for 5-HT_{1A}Rs in TLE. On the other hand, compelling pre-clinical and human studies have indicated an impairment of 5-HT_{1A} signal in this form of focal epilepsy and comorbid psychiatric disorders seen in these patients (Theodore et al. 2012). Indeed, recent imaging studies have shown a reduced serotonin 5-HT_{1A}R binding in temporal cortex and hippocampus of TLE patients (Giovacchini et al. 2005) that is correlated with scores on depression scales (Theodore et al. 2007) and memory impairment (Theodore et al. 2012). These findings are in agreement with the evidence that 5-HT_{1A} hypofunction induces hippocampal hyperexcitability (Chugani and Chugani 2003), reduces neoneurogenesis (Banasr et al. 2004) and hippocampal functional integrity (Chugani and Chugani 2003) and impairs memory processes (Ogren et al. 2008).

This work was proposed with the aim of clarifying the effect of 8-OH-DPAT in DG epileptogenesis using the in vivo acute MDA model of reverberatory epileptic activity in the hippocampal–parahippocampal circuits (Stringer and Lothman 1992). The results obtained here are in disagreement with those in kindled rats (Cagnotto et al. 1998; Watanabe et al. 1998). Indeed, we observed that acute-treated rats with 1 mg/kg of 8-OH-DPAT were resistant to the 'kindling-like' prolongation of electrographic seizure duration without affecting the time of onset of the paroxystic activity. It has been suggested that the latency to onset of MDA can be used as a gauge of seizure threshold; the duration of MDA can be used to measure of processes that terminate seizure activity in the limbic system. We found that systemic administration of 8-OH-DPAT produces a long-lasting effect (up to 4 h) similar to those obtained with conventional AEDs and MK-801 preventing the increase in duration of MDA, that is, kindling acquisition (Stringer and Lothman 1990a, b) but only partially suppressed kindled after discharges (at the 19th stimulation which shortened the duration of the MDA already established, Fig. 2a). Insofar as (1) AED treatments that inhibit the lengthening of evoked after discharges (analogous to MDA) have been considered antiepileptogenic (White 2002), and (2) that blockade of the 5-HT_{1A}R before and after pilocarpine treatment prevented seizure-induced hippocampal cell proliferation and survival but not the development of mossy fibre sprouting or spontaneously recurring seizures (Radley and Jacobs 2003), we cannot consider the inhibition of MDA prolongation (Figs. 1, 2) to be consistent with an antiepileptogenic role for the 5-HT_{1A}Rs. Taken together, our results with previous findings suggest that 5-HT_{1A}R activation is mostly antiepileptic.

In addition to the seizure model, we investigated the effects of 8-OH-DPAT (1 mg/kg, i.p.) for an effect on excitability, on paired-pulse interaction and on initiation of LTP in the DG with the aim of discovering the possible mechanisms responsible for the anticonvulsant actions of this high dose of the drug. We found that 8-OH-DPAT affects most of these parameters in a complex and diverse way. First, we tested the effect of 8-OH-DPAT on the slope of the fEPSP and the amplitude of the pSpikes which increased both by about 20 % 15 min after its administration, less pronounced effects compared to the +60 % increase elicited by 25 and 100 μg/kg of a previous early work (Klancnik et al. 1989). A possible explanation of our lower effects on population response is probably due to the fact that the high dose of 8-OH-DPAT produces a mixed activation of pre- and post-synaptic 5-HT_{1A}Rs while low doses are selectively acting on the autoreceptors within the raphe neurons (Klancnik et al. 1989). Consistently, 8-OH-DPAT induced inhibition of population responses in a dose-dependent manner in the DG in vitro (Klancnik et al. 1991) or when locally applied in the DG (Sanberg et al. 2006). Moreover, it is possible that high dose 8-OH-DPAT effects are mediated by the coactivation of 5-HT_7Rs, as recently results indicate this R subtype has a role in memory and hippocampal plasticity (Hedlund and Sutcliffe 2004; Costa et al. 2012a).

Nonetheless, it can be excluded that our results are due to the sample size of our experimental group since we confirmed them in the LTP experiments where again we measured these variables for 30 min before the tetanic stimulation, obtaining consistent results (Fig. 6b, c). Therefore, it seems that this high dose of 8-OH-DPAT produces a similar excitatory effect on basal activity at the PP synapse and between the synapse and the spike-generating mechanism in the granular layer (Richter-Levin and Segal 1990). We subsequently measured the reactivity of DG cells to increasing stimulation intensity of PP arising in the entorhinal cortex. There was no consistent shift of the stimulus intensity versus pSpike curve, stimulus intensity versus fEPSP slope curve or fEPSP slope versus pSpike amplitude (I/O) curve due to the drug treatment. These findings are surprising considering the excitatory effects seen in both the time course and the LTP experiments on slope and amplitude of pSpikes, possibly due to the different stimulatory protocol or the time gap used for the I/O curves to assess the potency of synaptic connections. The inhibitory trend that we revealed in the pSpike amplitude in our I/O experiments is in agreement with previous observations with 0.2 mg/kg, i.p. of 8-OH-DPAT (Levkovitz and Segal 1997); nevertheless, in our conditions this effect

never reached statistical significance. Moreover, we confirmed the lack of effect of lower doses of 8-OH-DPAT on the slope of the fEPSPs when systemically applied (Levkovitz and Segal 1997). However, it has to be noted that local application of 10 nmol of 8-OH-DPAT in DG produced a reduction of about 50 % in the slope 30 min after its application and a biphasical effect of pSpike amplitudes with a long-lasting decrease (Sanberg et al. 2006). Under our conditions, since that synaptic excitability is only slightly diminished in rats treated with a high dose of the drug, the likelihood that a cell will generate an action potential from a given synaptic drive remained unchanged (Fig. 3b). Therefore, 1 mg/kg of 8-OH-DPAT seems to be ineffective in changing integration of synaptic inputs to produce a DG action potential.

We subsequently measured the level of PPI within the dentate. In a previous in vivo study, intra hippocampal application of 8-OH-DPAT abolishes inhibition of the population spike observed in the second evoked response at intervals of 30–100 ms (Sanberg et al. 2006). In the present study, however, we observed different changes in paired-pulse relationships induced by its systemic administration. The triphasic pattern of paired-pulse interaction, illustrated in Fig. 5, is in full agreement with numerous earlier studies performed in the DG of rats anesthetized with urethane (Robinson and Racine 1986; Brucato et al. 1992). No effects were seen for early and late inhibition (IPI between 20–25 and >600 ms) while after the PPR in animals treated with the anticonvulsant dose of 1 mg/kg of 8-OH-DPAT showed no sign of paired-pulse facilitation (PPF) from the IPI of 40–150 ms although the difference was only significantly different for the two shorter intervals. Notwithstanding, early paired-pulse inhibition was seen when 8-OH-DPAT was injected in the DG of freely moving animals (Sanberg et al. 2006). Our study is the first to demonstrate loss of facilitation of PP-evoked pSpike amplitude produced by systemic 8-OH-DPAT. PPF and depression of the pSpike can give useful information about feedforward and feedback inhibitory circuits in the hippocampus (Bliss et al. 2007). If the first stimulus of a pair is able to evoke a pSpike, a $GABA_A$-mediated feedback inhibition lasting 10–20 ms prevents the second stimulus from evoking a pSpike. The spike facilitation at longer intervals may be explained by suppression of feedforward inhibition mediated by pre-synaptic $GABA_B$ autoreceptors (peak effect 100–200 ms). Thus, one possible reason for decreased PPF in 8-OH-DPAT-treated animals is a stronger feedforward inhibition, which may result from partial inhibition of feedback interneurons. It is worth noticing that hilar interneurons in DG represent a population of feedback interneurons (Freund and Buzsaki 1996) and express high levels of 5-HT_{1A}Rs (Azmitia et al. 1996) consistent with the evidence that serotonin inhibits hilar neurons (Misgeld et al. 1992), likely due to the activation of 5-HT_{1A}Rs. Finally, to further evaluate the effect of the anticonvulsant dose of 8-OH-DPAT on hippocampal plasticity, we studied the PP-DG LTP induced by strong HSF. It is well known that the activation of 5-HT_{1A}Rs by 5-HT is crucial for inducing LTP (Sanberg et al. 2006). In our condition, the drug pre-treatment induced a significant potentiation of the pSpike amplitude even when we subtracted the baseline excitatory effect exerted by 1 mg/kg 8-OH-DPAT, while the slope of the fEPSP was only slightly increased. It is noteworthy that systemic administration of the 0.3 mg/kg of 8-OH-DPAT or its local application in the MRN has been shown to attenuate dentate LTP induction while its injection in the DG was ineffective (Sanberg et al. 2006). This evidence suggests that the effect of 8-OH-DPAT must be mediated by the activation of 5-HT_{1A}Rs external to the DG, for example, on raphe nuclei which are highly sensitive to 8-OH-DPAT (Jolas et al. 1995) and consequent reduction in the inhibitory 5-HT tone (Crespi 2010) on GABAergic interneurons. Moreover, activation of the 5-HT_{1A}R inhibits the induction of LTP in DG in slice preparation (Sakai and Tanaka 1993; Grzegorzewska et al. 2010). Nevertheless, the dose of 8-OH-DPAT used in this study produced a clear-cut and significant increase in the LTP of the pSpike amplitude; the exact mechanisms and brain sites through which this potentiation occurs obviously need further evaluation. It might be possible that with a high dose of 8-OH-DPAT, a stronger post-synaptic activation could be produced unmasking hyperpolarization of interneurons and reducing GABA release at the level of the PP-DG synapse. Moreover, the 5-HT_7 involvement cannot be excluded, although no data on its role on granular cells excitability are available yet.

Consistent with the relatively dense serotonergic innervation of interneuron regions of the DG, the present study finds that 1 mg/kg of 8-OH-DPAT is anticonvulsant and reduces the MDA probably by an augmentation of interneuron circuit activity. The principal findings of our study are that 8-OH-DPAT affects the reactivity and short- and long-term plasticity of the PP-DG synapse, potentiating pSpike amplitude and the slope of fEPSP under normal condition and increased LTP through a possible 5-HT_{1A} mechanism. Thus, our results suggest that 8-OH-DPAT at high dose might be useful not only in the control of epileptic seizures but also in the comorbid memory impairments which occur not infrequently in patients with epilepsy, especially with TLE (Bell et al. 2011). These positive cognitive effects together with the possible antidepressant properties of 5-HT_{1A} agonists including 8-OH-DPAT (Lacivita et al. 2008) and the antiepileptic activity shown here may offer new therapeutic possibilities (Lacivita et al. 2012) for an old drug.

Acknowledgments This study was supported by University of Malta research funding scheme, coordinator G. Di Giovanni. G.O. is supported by MIUR, Italy.

References

Azmitia EC, Gannon PJ, Kheck NM, Whitaker-Azmitia PM (1996) Cellular localization of the 5-HT1A receptor in primate brain neurons and glial cells. Neuropsychopharmacology 14:35–46

Banasr M, Hery M, Printemps R, Daszuta A (2004) Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology 29:450–460

Bell B, Lin JJ, Seidenberg M, Hermann B (2011) The neurobiology of cognitive disorders in temporal lobe epilepsy. Nat Rev Neurol 7:154–164

Bliss TV, Lomo T (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. J Physiol 232:331–356

Bliss T, Collingridge G, Morris R (2007) Synaptic plasticity in the hippocampus. In: Pea Andersen (ed) The hippocampus book. Oxford University Press, New York

Bombardi C, Di Giovanni G (2013) Functional anatomy of 5-HT receptors in the amygdala and hippocampal complex: relevance to memory functions. Exp Brain Res. doi:10.1007/s00221-013-3512-6 (in press)

Bortolato M, Pivac N, Mück-Šeler D, Nikolac Perkovic M, Pessia M, Di Giovanni G (2013) The role of the serotonergic system at the interface of aggression and suicide. Neuroscience 236:160–185

Bough KJ, Schwartzkroin PA, Rho JM (2003) Calorie restriction and ketogenic diet diminish neuronal excitability in rat dentate gyrus in vivo. Epilepsia 44:752–760

Brucato FH, Morrisett RA, Wilson WA, Swartzwelder HS (1992) The GABAB receptor antagonist, CGP-35348, inhibits paired-pulse disinhibition in the rat dentate gyrus in vivo. Brain Res 588:150–153

Cagnotto A, Crespi D, Mancini L, Manzoni C, Presti ML, Gariboldi M, Vezzani A, Mennini T (1998) Lasting increase in serotonin 5-HT1A but not 5-HT4 receptor subtypes in the kindled rat dentate gyrus: dissociation from local presynaptic effects. J Neurochem 70:850–857

Chugani DC, Chugani HT (2003) Does serotonin have trophic effects in temporal lobe epilepsy? Neurology 60:736–737

Clinckers R, Smolders I, Meurs A, Ebinger G, Michotte Y (2004) Anticonvulsant action of hippocampal dopamine and serotonin is independently mediated by D2 and 5-HT1A receptors. J Neurochem 89:834–843

Collins RC, Tearse RG, Lothman EW (1983) Functional anatomy of limbic seizures: focal discharges from medial entorhinal cortex in rat. Brain Res 280:25–40

Costa L, Spatuzza M, D'Antoni S, Bonaccorso CM, Trovato C, Musumeci SA, Leopoldo M, Lacivita E, Catania MV, Ciranna L (2012a) Activation of 5-HT7 serotonin receptors reverses metabotropic glutamate receptor-mediated synaptic plasticity in wild-type and Fmr1 knockout mice, a model of Fragile X syndrome. Biol Psychiatry 72:924–933

Costa L, Trovato C, Musumeci SA, Catania MV, Ciranna L (2012b) 5-HT(1A) and 5-HT(7) receptors differently modulate AMPA receptor-mediated hippocampal synaptic transmission. Hippocampus 22:790–801

Crespi F (2010) SK channel blocker apamin attenuates the effect of SSRI fluoxetine upon cell firing in dorsal raphe nucleus: a concomitant electrophysiological and electrochemical in vivo study reveals implications for modulating extracellular 5-HT. Brain Res 1334:1–11

Di Giovanni G, Di Matteo V, Esposito E (eds) (2008) Serotonin–dopamine interaction: experimental evidence and therapeutic relevance. Elsevier, Amsterdam

Freund TF (1992) GABAergic septal and serotonergic median raphe afferents preferentially innervate inhibitory interneurons in the hippocampus and dentate gyrus. Epilepsy Res Suppl 7:79–91

Freund TF, Buzsaki G (1996) Interneurons of the hippocampus. Hippocampus 6:347–470

Freund TF, Gulyas AI, Acsady L, Gorcs T, Toth K (1990) Serotonergic control of the hippocampus via local inhibitory interneurons. Proc Natl Acad Sci USA 87:8501–8505

Garcia CS (2012) Depression in temporal lobe epilepsy: a review of prevalence, clinical features, and management considerations. Epilepsy Res Treat 2012:809843

Gariboldi M, Tutka P, Samanin R, Vezzani A (1996) Stimulation of 5-HT1A receptors in the dorsal hippocampus and inhibition of limbic seizures induced by kainic acid in rats. Br J Pharmacol 119:813–818

Giovacchini G, Toczek MT, Bonwetsch R, Bagic A, Lang L, Fraser C, Reeves-Tyer P, Herscovitch P, Eckelman WC, Carson RE, Theodore WH (2005) 5-HT 1A receptors are reduced in temporal lobe epilepsy after partial-volume correction. J Nucl Med 46:1128–1135

Grzegorzewska M, Mackowiak M, Wedzony K, Hess G (2010) 5-HT1A receptors mediate detrimental effects of cocaine on long-term potentiation and expression of polysialylated neural cell adhesion molecule protein in rat dentate gyrus. Neuroscience 166:122–131

Gulyas AI, Acsady L, Freund TF (1999) Structural basis of the cholinergic and serotonergic modulation of GABAergic neurons in the hippocampus. Neurochem Int 34:359–372

Hedlund PB, Sutcliffe JG (2004) Functional, molecular and pharmacological advances in 5-HT7 receptor research. Trends Pharmacol Sci 25:481–486

Heinemann U, Beck H, Dreier JP, Ficker E, Stabel J, Zhang CL (1992) The dentate gyrus as a regulated gate for the propagation of epileptiform activity. Epilepsy Res Suppl 7:273–280

Jolas T, Schreiber R, Laporte AM, Chastanet M, De Vry J, Glaser T, Adrien J, Hamon M (1995) Are postsynaptic 5-HT1A receptors involved in the anxiolytic effects of 5-HT1A receptor agonists and in their inhibitory effects on the firing of serotonergic neurons in the rat? J Pharmacol Exp Ther 272:920–929

Kanner AM, Balabanov A (2002) Depression and epilepsy: how closely related are they? Neurology 58:S27–S39

Klancnik JM, Baimbridge KG, Phillips AG (1989) Increased population spike amplitude in the dentate gyrus following systemic administration of 5-hydroxytryptophan or 8-hydroxy-2-(di-*n*-propylamino)tetralin. Brain Res 505:145–148

Klancnik JM, Obenaus A, Phillips AG, Baimbridge KG (1991) The effects of serotonergic compounds on evoked responses in the dentate gyrus and CA1 region of the hippocampal formation of the rat. Neuropharmacology 30:1201–1209

Lacivita E, Leopoldo M, Berardi F, Perrone R (2008) 5-HT1A receptor, an old target for new therapeutic agents. Curr Top Med Chem 8:1024–1034

Lacivita E, Di Pilato P, De Giorgio P, Colabufo NA, Berardi F, Perrone R, Leopoldo M (2012) The therapeutic potential of 5-HT1A receptors: a patent review. Expert Opin Ther Pat 22:887–902

Levkovitz Y, Segal M (1997) Serotonin 5-HT1A receptors modulate hippocampal reactivity to afferent stimulation. J Neurosci 17:5591–5598

Lopez-Meraz ML, Gonzalez-Trujano ME, Neri-Bazan L, Hong E, Rocha LL (2005) 5-HT1A receptor agonists modify epileptic seizures in three experimental models in rats. Neuropharmacology 49:367–375

Lopez-Meraz ML, Martinez A, Rocha L (2007) Effect of 8-OH-DPAT on electrographic activity during the kainic acid-induced status epilepticus in rats. Seizure 16:365–370

Lovenberg TW, Baron BM, de Lecea L, Miller JD, Prosser RA, Rea MA, Foye PE, Racke M, Slone AL, Siegel BW et al (1993) A novel adenylyl cyclase-activating serotonin receptor (5-HT7) implicated in the regulation of mammalian circadian rhythms. Neuron 11:449–458

Misgeld U, Bijak M, Brunner H (1992) Granule cell inhibition and the activity of hilar neurons. Epilepsy Res Suppl 7:113–118

Motamedi GK, Meador KJ (2004) Antiepileptic drugs and memory. Epilepsy Behav 5:435–439

Ogren SO, Eriksson TM, Elvander-Tottie E, D'Addario C, Ekstrom JC, Svenningsson P, Meister B, Kehr J, Stiedl O (2008) The role of 5-HT(1A) receptors in learning and memory. Behav Brain Res 195:54–77

Paxinos G, Watson C (1986) The rat brain in stereotaxic coordinates. Academic Press, Sydney, Australia

Pazos A, Palacios JM (1985) Quantitative autoradiographic mapping of serotonin receptors in the rat brain. I. Serotonin-1 receptors. Brain Res 346:205–230

Radley JJ, Jacobs BL (2003) Pilocarpine-induced status epilepticus increases cell proliferation in the dentate gyrus of adult rats via a 5-HT1A receptor-dependent mechanism. Brain Res 966:1–12

Richter-Levin G, Segal M (1990) Effects of serotonin releasers on dentate granule cell excitability in the rat. Exp Brain Res 82:199–207

Robinson GB, Racine RJ (1986) Interactions between septal and entorhinal inputs to the rat dentate gyrus: facilitation effects. Brain Res 379:63–67

Sakai N, Tanaka C (1993) Inhibitory modulation of long-term potentiation via the 5-HT1A receptor in slices of the rat hippocampal dentate gyrus. Brain Res 613:326–330

Salgado D, Alkadhi KA (1995) Inhibition of epileptiform activity by serotonin in rat CA1 neurons. Brain Res 669:176–182

Salgado-Commissariat D, Alkadhi KA (1997) Serotonin inhibits epileptiform discharge by activation of 5-HT1A receptors in CA1 pyramidal neurons. Neuropharmacology 36:1705–1712

Sanberg CD, Jones FL, Do VH, Dieguez D Jr, Derrick BE (2006) 5-HT1a receptor antagonists block perforant path-dentate LTP induced in novel, but not familiar, environments. Learn Mem 13:52–62

Scharfman HE (ed) (2007) The dentate gyrus: a comprehensive guide to structure, function, and clinical implications. Elsevier, Amsterdam

Sharp T, Hjorth S (1990) Application of brain microdialysis to study the pharmacology of the 5-HT1A autoreceptor. J Neurosci Methods 34:83–90

Stringer JL, Erden F (1995) In the hippocampus in vivo, nitric oxide does not appear to function as an endogenous antiepileptic agent. Exp Brain Res 105:391–401

Stringer JL, Lothman EW (1990a) Maximal dentate activation: a tool to screen compounds for activity against limbic seizures. Epilepsy Res 5:169–176

Stringer JL, Lothman EW (1990b) Use of maximal dentate activation to study the effect of drugs on kindling and kindled responses. Epilepsy Res 6:180–186

Stringer JL, Lothman EW (1992) Reverberatory seizure discharges in hippocampal–parahippocampal circuits. Exp Neurol 116:198–203

Stringer JL, Sowell KL (1994) Kainic acid, bicuculline, pentylenetetrazol and pilocarpine elicit maximal dentate activation in the anesthetized rat. Epilepsy Res 18:11–21

Stringer JL, Williamson JM, Lothman EW (1989) Induction of paroxysmal discharges in the dentate gyrus: frequency dependence and relationship to afterdischarge production. J Neurophysiol 62:126–135

Theodore WH (2003) Does serotonin play a role in epilepsy? Epilepsy Curr 3:173–177

Theodore WH, Hasler G, Giovacchini G, Kelley K, Reeves-Tyer P, Herscovitch P, Drevets W (2007) Reduced hippocampal 5HT1A PET receptor binding and depression in temporal lobe epilepsy. Epilepsia 48:1526–1530

Theodore WH, Wiggs EA, Martinez AR, Dustin IH, Khan OI, Appel S, Reeves-Tyer P, Sato S (2012) Serotonin 1A receptors, depression, and memory in temporal lobe epilepsy. Epilepsia 53:129–133

Tokarski K, Zahorodna A, Bobula B, Hess G (2002) Comparison of the effects of 5-HT1A and 5-HT4 receptor activation on field potentials and epileptiform activity in rat hippocampus. Exp Brain Res 147:505–510

Wada Y, Nakamura M, Hasegawa H, Yamaguchi N (1992) Role of serotonin receptor subtype in seizures kindled from the feline hippocampus. Neurosci Lett 141:21–24

Wada Y, Nakamura M, Hasegawa H, Yamaguchi N (1993) Intra-hippocampal injection of 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) inhibits partial and generalized seizures induced by kindling stimulation in cats. Neurosci Lett 159:179–182

Watanabe K, Minabe Y, Ashby CR Jr, Katsumori H (1998) Effect of acute administration of various 5-HT receptor agonists on focal hippocampal seizures in freely moving rats. Eur J Pharmacol 350:181–188

White HS (2002) Animal models of epileptogenesis. Neurology 59:S7–S14