ELSEVIER

Pharmacology, Biochemistry and Behavior 69 (2001) 367–372

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Different effects of anxiolytic agents, diazepam and 5-HT_{1A} agonist tandospirone, on hippocampal long-term potentiation in vivo

Kiyoshi Mori*, Hiroko Togashi, Taku Kojima, Machiko Matsumoto, Satoshi Ohashi, Ken-ichi Ueno, Mitsuhiro Yoshioka

Department of Pharmacology, Hokkaido University School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan

Received 7 September 2000; received in revised form 16 January 2001; accepted 19 February 2001

Abstract

Benzodiazepines and 5-HT_{1A} agonists have been widely used as anxiolytic agents. Some clinical reports document that 5-HT_{1A} agonists induce memory impairment to a lesser degree than diazepam. In the present study, we compared the effects of diazepam and 5-HT_{1A} agonist, tandospirone, on hippocampal long-term potentiation (LTP) in Schaffer collateral-CA1, mossy fiber-CA3 and perforant path-dentate gyrus synapses. In the diazepam-injected group, the reduction in LTP was observed in all three types of synapses, although the effective dose differed among these. In the tandospirone-injected group, no reduction in LTP was observed except in Schaffer-CA1 synapses. In addition, population spike amplitude was potentiated by tandospirone in mossy fiber-CA3 synapses in a dose-dependent manner. Thus, there was a discrepancy in the effects on hippocampal LTP between diazepam and tandospirone, possibly reflecting the reported clinical properties of these drugs, in that 5-HT_{1A} partial agonists do not affect learning and memory, whereas diazepam impairs memory function.

Keywords: Long-term potentiation (LTP); Hippocampus; Diazepam; Tandospirone; Fear-conditioning

1. Introduction

Gamma-amino butyric acid (GABA) and serotonin (5-HT) have been extensively used as anxiolytic agents. Benzodiazepines, the classical anxiolytic agents usually administered upon clinical signs of anxiety, panic and epilepsy, bind to $GABA_A$ receptors at the benzodiazepine recognition site and enhance the inhibitory effects of GABA. 5-HT has been implicated in the control of a wide variety of psychiatric functions, with dysfunction of the 5-HT system thought to be involved in the development and/or progression of neuropsychiatric disorders including depression and anxiety (Duman, 1998; Graeff et al., 1996). Previous studies have clarified the physiological and pharmacological aspects of 5-HT receptor subtypes. Among these, 5-HT_{1A} receptors have attracted the most attention, because the clinically effective anxiolytic agent, buspirone, is a 5-HT_{1A} receptor partial agonist (New, 1990; Tunnicliff, 1991) and because knockout mice lacking 5-HT_{1A} receptors showed an increased tendency to avoid stressful situations (Parks et al., 1998; Ramboz et al., 1998). These results suggest that 5-HT_{1A} receptors play an important role in modifying psychiatric functions. However, a number of studies reported amnesia as a common side effect of treatment with classical benzodiazepines such as diazepam in humans (Lister, 1985) and other species (Izquierdo et al., 1990; Sarter et al., 1995; Venault et al., 1986), whereas some clinical studies have shown that a 5-HT_{1A} partial agonist, the clinically effective anxiolytic buspirone, did not induce impairment of learning or memory (Hart et al., 1991; Lawlor et al., 1992; Lucki et al., 1987).

Hippocampal long-term potentiation (LTP) has been suggested to be the electrophysiological basis of learning and memory. Hippocampal LTP is expressed in the input–output pathways of the hippocampus, i.e., the entorhinal cortex to dentate granule cells, granule cells to CA3 pyramidal cells and CA3 pyramidal cells to CA1 pyramidal cells (Kelso et al., 1986; Steward, 1976). In these trisynaptic circuits, different synaptic mechanisms are responsible for the induction and maintenance of LTP. The induction of LTP in the Schaffer-collateral CA1 and the perforant path-dentate

* Corresponding author. Tel.: +81-11-706-5058; fax: +81-11-706-7872.
E-mail address: kimori@med.hokudai.ac.jp (K. Mori).

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00546-9

gyrus synapses is dependent on NMDA receptors. In contrast, LTP in mossy fiber-CA3 synapses is independent of NMDA receptors and the induction of LTP instead requires an increase in cAMP (Manabe, 1997; Zalutsky and Nicoll, 1990). It is therefore possible that not only the mechanisms but also the functional roles of LTP differ among hippocampal synapses.

In the present study, we investigated whether hippocampal LTP reflects the clinical properties previously reported following administration of benzodiazepines and 5-HT_{1A} agonists, i.e., the induction and non-induction of memory impairment, respectively. The effects of a classical benzodiazepine, diazepam, and of the 5-HT_{1A} agonist, tandospirone, on LTP in the Schaffer collateral-CA1, mossy fiber-CA3 and perforant path-dentate gyrus synapses were comparatively evaluated.

2. Methods

2.1. Animals

Male Wistar rats (280–410 g and 8–13 weeks old) were used (Slc:Wistar/ST, Shizuoka Laboratory Animal Center, Hamamatsu, Japan). The animals were housed in a room with a 12-h light–dark cycle and were given free access to food and water. These studies were conducted in accordance with the standards established by the Guide for the Care and Use of Laboratory Animals of the Hokkaido University School of Medicine.

2.2. Evaluation of fear-related behavior

A chamber (30 × 30 × 27 cm) constructed from aluminum (sidewalls) and Plexiglas (rear wall, ceiling and front door) was used in order to evaluate fear-related behavior. The floor of the chamber consisted of 27 stainless steel rods wired to a shock generator that delivered foot shocks.

On day 1, rats were exposed to the chamber for 3 min. After exploration of the new environment, rats were given three foot shocks (2 s, 0.5 mA, 30 s intervals). Thirty seconds after the final shock, the rats were returned to their home cages. On day 2, saline (5.0 ml/kg i.p., control) or either of the anxiolytic drugs diazepam (0.5 mg/kg i.p.) or tandospirone (1.0 mg/kg i.p.) were injected. Twenty minutes after injection, rats were reexposed to the chamber, and freezing behavior was counted at 5-s intervals over a period of 30 min. Freezing was defined as the absence of all movement, with the exception of those related to respiration. The percentage of freezing was calculated every 5 min.

2.3. Measurement of LTP

LTP was measured as previously described (Mori et al., 1998). The rats were tracheotomized, artificially respirated with 1% halothane and fixed in a stereotaxic frame. During recording of LTP, heart rate and blood pressure were monitored. Stainless steel bipolar stimulating electrodes were inserted into the Schaffer collateral, mossy fiber or the perforant path region. A monopolar recording electrode was placed in the pyramidal cell layer of CA1, the pyramidal cell layer of CA3 or the granule cell layer of the dentate gyrus. Single test stimuli were delivered at intervals of 30 s and an average of five responses was obtained every 5 min. After test stimuli were delivered for 20 min, saline or either diazepam or tandospirone were injected intraperitoneally. At 20 min postinjection, high-frequency stimuli were delivered. These tetanic stimuli consisted of 5 or 10 trains at 1 Hz, each composed of eight pulses at 400 Hz. Following stimulation, the changes in the amplitude of the population spike were measured for 1 h. In each synapse, the time course of changes and the area under the curve (AUC) from 0 to 60 min were evaluated.

2.4. Statistical analysis

Statistical differences between group means were determined by analysis of variances, followed by Bonferroni-adjusted t tests. Differences were considered significant at the $P < .05$ level.

3. Results

3.1. Effects on fear-related behavior

Fear-conditioning was conducted to confirm the anxiolytic effects of diazepam and tandospirone. Diazepam (0.5 mg/kg i.p.) and tandospirone (1.0 mg/kg i.p.) were administered 20 min before rats were re-exposed to the foot shock chamber. Administration of diazepam and tandospirone

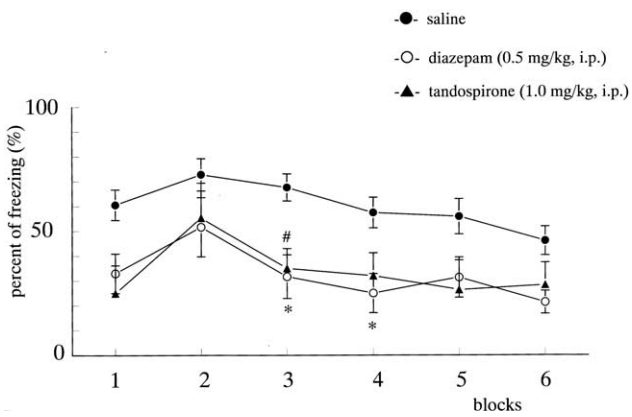

Fig. 1. Administration of diazepam (0.5 mg/kg) and tandospirone (1 mg/kg) reduced the freezing behavior of rats in fear conditioning. The anxiolytic effects were comparable between these anxiolytic agents. ●–●, saline-injected group ($n = 8$); ○–○, 0.5 mg/kg diazepam-injected group ($n = 5$); ▲–▲, 1 mg/kg tandospirone-injected group ($n = 5$). * $P < .05$, diazepam- vs. saline-injected group . # $P < .05$, tandospirone- vs. saline-injected group.

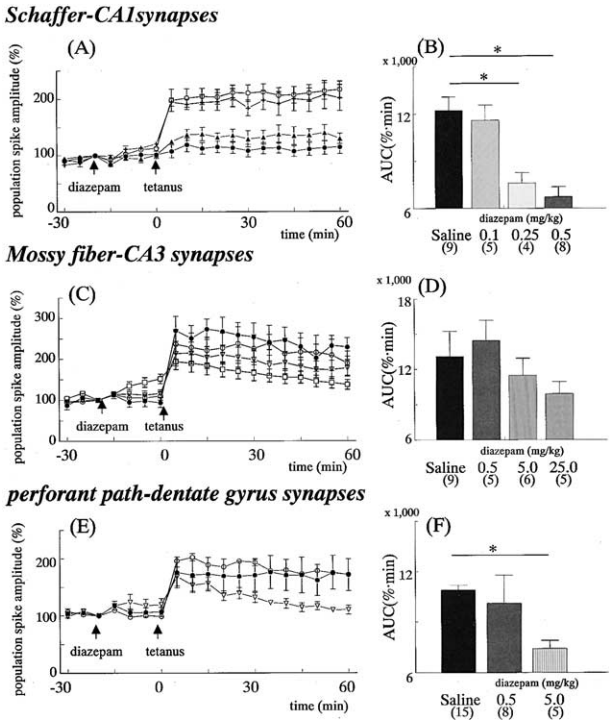

Fig. 2. Effects of diazepam on time course of population spike amplitude changes and AUC from 0 to 60 min in Schaffer-CA1 (A, B), mossy fiber-CA3 (C, D) and perforant path-dentate gyrus (E, F) synapses. In these three types of synapses, LTP was reduced in a dose-dependent manner. (A) In Schaffer-CA1 synapses, induction of LTP was inhibited by injection of 0.25 mg/kg diazepam. (B) The reduction in LTP by 0.25 and 0.5 mg/kg diazepam was statistically significant in AUC analysis. (C) In mossy fiber-CA3 synapses, LTP was inhibited by 25 mg/kg diazepam. (D) A dose-dependent reduction in LTP by injection of diazepam was observed, although the inhibition was not statistically significant. (E) In perforant path-dentate gyrus synapses, induction of LTP was not changed, but maintenance of LTP was inhibited by 5 mg/kg diazepam. (F) The reduction in LTP by injection of 5 mg/kg diazepam was statistically significant. The numbers in parentheses in B, D and F are the numbers of animals examined. ○–○, saline-injected group in A, C, E; +–+, 0.1 mg/kg diazepam group in A; ▲–▲, 0.25 mg/kg diazepam group in A; ●–●, 0.5 mg/kg diazepam group in A, C, E; □–□, 5 mg/kg diazepam group in C, E; ▽–▽, 25 mg/kg diazepam group in C. $*P<.05$, compared with the saline-injected group.

significantly reduced the incidence of freezing behavior compared with the saline-injected control group (Fig. 1). The anxiolytic effects were comparable between the diazepam- and tandospirone-injected groups at doses of 0.5 and 1.0 mg/kg, respectively.

3.2. Effects on LTP

After tetanic stimulation, each population spike amplitude was potentiated in the control group. Following the administration of diazepam (0.1–25 mg/kg) 20 min before tetanic stimulation, LTP was reduced in a dose-dependent manner in all three types of synapses. In Schaffer-CA1 synapses, induction of LTP was inhibited by injection of 0.25 mg/kg diazepam. The reduction in LTP by 0.25 and 0.5 mg/kg diazepam was statistically significant in AUC analysis (Fig. 2A, B). In mossy fiber-CA3 synapses, LTP was inhibited by 25 mg/kg diazepam. A dose-dependent reduction in LTP by injection of diazepam was observed, although the inhibition was not statistically significant (Fig. 2C, D). In perforant path-dentate gyrus synapses, induction of LTP remained unchanged, but maintenance of LTP was inhibited by 5 mg/kg diazepam. The reduction in LTP by injection of 5 mg/kg diazepam was statistically significant (Fig. 2E, F). Thus, diazepam reduced hippocampal LTP in all three types of synapses examined, although the effective doses were different.

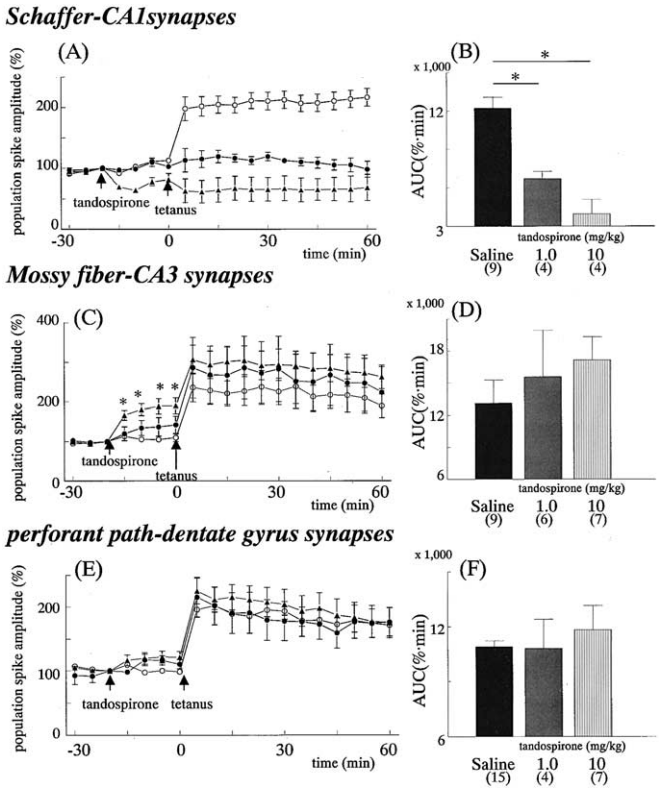

Fig. 3. Effects of tandospirone on time course of population spike amplitude changes and AUC from 0 to 60 min in Schaffer-CA1 (A, B), mossy fiber-CA3 (C, D) and perforant path-dentate gyrus synapses (E, F). Effects of tandospirone differed in a synapse-dependent manner. (A) In Schaffer-CA1 synapses, induction of LTP was inhibited by injection of 1 mg/kg tandospirone. The population spike amplitude was reduced by 10 mg/kg tandospirone. (B) The reduction in LTP by 1 and 10 mg/kg tandospirone was statistically significant in AUC analysis. (C) In mossy fiber-CA3 synapses, LTP and population spike amplitude were facilitated in a dose-dependent manner. (D) A dose-dependent facilitation of LTP by injection of tandospirone was observed, although the facilitation was not statistically significant. (E) In perforant path-dentate gyrus synapses, LTP was not affected by tandospirone. (F) LTP was not influenced by tandospirone in AUC analysis. The numbers in parentheses in B, D and F are the numbers of animals examined. ○–○, saline-injected group; ●–●, 1 mg/kg tandospirone group; ▲–▲, 10 mg/kg tandospirone group. $*P<.05$, compared with the saline-injected group.

3.3. Effects of tandospirone

Tandospirone (1.0 and 10 mg/kg i.p.) was injected intraperitoneally 20 min before tetanic stimulation. Effects of tandospirone differed in a synapse-dependent manner. In Schaffer-CA1 synapses, induction of LTP was inhibited by injection of 1 mg/kg tandospirone. The population spike amplitude was reduced by 10 mg/kg tandospirone. The reduction in LTP by 1 and 10 mg/kg tandospirone was statistically significant in AUC analysis (Fig. 3A, B). In mossy fiber-CA3 synapses, LTP and population spike amplitude were facilitated in a dose-dependent manner, although the facilitation was not statistically significant (Fig. 3C, D). In perforant path-dentate gyrus synapses, LTP was unaffected by tandospirone (Fig. 3E, F). Thus, tandospirone reduced population spike amplitude both before and after tetanic stimulation only in Schaffer-CA1 synapses. On the other hand, it facilitated both in mossy fiber-CA3 synapses in a dose-dependent manner.

4. Discussion

In the present study, behavioral experiments were carried out in addition to electrophysiological ones in order to indicate the anxiolytic activity of these agents in the dose ranges used in the LTP experiments. All rats injected with the benzodiazepine, diazepam (0.5 mg/kg i.p.) or the 5-HT_{1A} agonist, tandospirone (1 mg/kg i.p.) showed reduced fear-related freezing behavior in the conditioning chamber, compared with controls, confirming that both drugs possess anxiolytic ability. We preliminarily studied the effects of high-dose diazepam (5 mg/kg i.p.) and tandospirone (10 mg/kg i.p.) on fear-related behavior. In both groups, various side effects, i.e., muscle relaxation by diazepam, flat-body posture and the hypolocomotion by tandospirone, were observed. Thus, we did not consider that it was possible to exactly evaluate anxiolytic effects in both high-dose diazepam and tandospirone.

In the diazepam-injected group, the induction of LTP in Schaffer-CA1 synapses as well as the maintenance of LTP in mossy fiber-CA3 and perforant path-dentate gyrus synapses were reduced. The pharmacological effects of benzodiazepines are mediated by binding to a recognition site of the benzodiazepine–$GABA_A$ receptor complex. These receptors gate fast inhibitory synaptic transmission via an integral chloride ion channel. Previous reports that $GABA_A$ agonists suppress LTP induction (Del Cerro et al., 1992; Evans and Viola-McCabe, 1995) and that $GABA_A$ antagonists facilitate it (Seabrook et al., 1997) in the CA1 region in vitro suggest that LTP might be controlled by $GABA_A$-mediated inhibitory mechanisms. Our observation that diazepam suppressed hippocampal LTP in the CA1 region is consistent with these previous reports. However, it was noted that effective doses differed among the three types of synapses examined. In the CA3 region, differences in the mechanism of LTP induction might be responsible for sensitivity to diazepam. However, in the present study, the induction of LTP was inhibited in Schaffer-CA1 synapses, whereas only the maintenance of LTP was inhibited in perforant path-dentate gyrus synapses, although both mechanisms of LTP induction are mediated by NMDA receptors. The reason for this was not clarified, but this finding may indicate that the involvement of $GABA_A$ receptors in LTP induction differs between Schaffer-CA1 and perforant path-dentate gyrus synapses.

Tandospirone influenced hippocampal LTP in a synapse-dependent manner in the present study. In Schaffer-CA1 synapses, the induction of LTP was reduced by 1 mg/kg tandospirone, and the population spike amplitude before tetanic stimulation was also suppressed by 10 mg/kg tandospirone. In contrast, both were potentiated in mossy fiber-CA3 synapses in a dose-dependent manner. In perforant path-dentate gyrus synapses, tandospirone did not affect the induction or maintenance of LTP.

Intracellular recordings from hippocampal CA1 pyramidal cells in vitro have shown that exogenously applied 5-HT produces both inhibitory and excitatory effects (Andrade and Nicoll, 1987; Colino and Hallowell, 1987; Corradetti et al., 1992). In the CA1 region, previous studies have demonstrated that 5-HT decreases excitatory postsynaptic potentials by eliciting a 5-HT_{1A} receptor-mediated increase in potassium conductance (Anwyl, 1990). In addition, peripheral application of 5-HT_{1A} receptor agonists reportedly primarily activated the somadendritic 5-HT_{1A} autoreceptors and caused suppression of the firing rate in the raphe nucleus (Dong et al., 1997; Godbout et al., 1991). Since the hippocampal CA1 pyramidal cells receive afferent fibers from the raphe area, reduction in the firing rate in the raphe nucleus might suppress population spike amplitude. Our results were consistent with those of previous studies, indicating that 8-OH-DPAT, a 5-HT_{1A} agonist, suppressed the population spike amplitude in Schaffer-CA1 synapses of hippocampal slices (Bijak et al., 1996).

In mossy fiber-CA3 synapses, the population spike amplitude both before and after tetanic stimulation was increased after administration of tandospirone in the present study. LTP in mossy fiber-CA3 synapses is NMDA receptor-independent and is triggered by a rise in intracellular calcium levels and subsequent formation of cAMP in the mossy presynaptic terminals. Since 5-HT_{1A} receptors are considered to be coupled with Gi-protein and decrease cAMP levels (Gerhardt and Heerikhuizen, 1997; Lucas and Hen, 1995), we assumed that the population spike amplitude in mossy fiber-CA3 synapses might be reduced by the application of tandospirone. The reasons why the population spike amplitude was increased by administration of the 5-HT_{1A} agonist, tandospirone remain to be determined. Mossy fibers make synaptic contact with inhibitory interneurons, and the number of their connections is 200- to 2000-fold greater than those between mossy fibers and CA3 pyramidal cells (Gulyas et al., 1992). It is possible that the

changes in population spikes observed in mossy fiber-CA3 synapses may be related to inhibitory interneurons. 5-HT has been reported to suppress inhibitory interneurons via 5-HT_{1A} receptors (Schmitz et al., 1995), with 5-HT_{1A} agonists increasing cAMP levels in the hippocampus (Markstein et al., 1999). The LTP-like changes in the mossy fiber-CA3 synapses may therefore be attributable to the tandospirone-induced increase in cAMP levels in the CA3 area.

In perforant path-dentate gyrus synapses, we found that even the highest dose of tandospirone did not influence induction or maintenance of LTP. LTP in the CA1 region might be more sensitive to 5-HT than that in the dentate gyrus region, although both mechanisms of LTP are thought to be identical. The reason for the differential effects of tandospirone is less clear, although they are known to be due to the influences of the dopamine and adrenergic systems, which interact with 5-HT in the hippocampus. The contribution of dopamine D1/D5 receptors and β-adrenergic receptors to LTP reportedly differ between the CA1 and the dentate gyrus region (Swanson-Park et al., 1999). Tandospirone might moderate the dopamine and adrenergic systems, which in turn would induce the dissociation of LTP between CA1 and the dentate gyrus.

During exploratory behavior, rhythmic firing is recorded only in granule cells of the dentate gyrus, and at the end of exploration synchronized firing is observed in pyramidal cells in CA3 and CA1 (Buzsáki, 1989). According to this two-staged model proposed by Buzsáki, the rapid firing in the dentate gyrus might provide the neural basis of the fragile memory trace, and the synchronized firing in pyramidal cells in CA3 and CA1 might form the enduring memory trace. Thus, the formation of LTP in perforant path-dentate gyrus synapses might be required for fragile learning and memory. On the basis of this hypothesis, the present observation that tandospirone did not affect LTP, whereas diazepam reduced LTP in the dentate gyrus, might explain the clinical evidence that acute benzodiazepine intake impairs memory function, whereas 5-HT_{1A} agonists do not.

In the present study, the effects of two major anxiolytic agents on hippocampal LTP in three types of synapses were investigated. LTP in only schaffer-CA1 synapses was reduced by tandospirone, whereas LTP was reduced throughout the hippocampus upon the administration of diazepam. These differences might reflect the clinical evidence that 5-HT_{1A} agonists do not impair learning and memory.

References

Andrade R, Nicoll RA. Pharmacologically distinct actions of serotonin on signal pyramidal neurons of the rat hippocampus recorded in vitro. J Physiol 1987;394:99–124.

Anwyl R. Neurophysiological action of 5-hydroxytryptamine in the vertebrate nervous systems. Prog Neurobiol 1990;35:451–68.

Bijak M, Tokarski K, Czyrak A, Mackowiak M, Wedzony K. Imipramine increases the 5-HT_{1A} receptor-mediated inhibition of hippocampal neurons without changing the 5-HT_{1A} receptor binding. Eur J Pharmacol 1996;305:79–85.

Buzsáki G. Two-stage model of memory trace formation a role for "noisy" brain state. Neuroscience 1989;31(3):551–70.

Corradetti R, Ballenriti L, Pugliese AM, Pepeu G. Serotonin blocks the long-term potentiation induced by primed bust stimulation in the CA1 region of rat hippocampal slices. Neuroscience 1992;40:399–412.

Colino A, Hallowell JV. Differential modulation of three separate K-conductances in hippocampal CA1 neurons by serotonin. Nature 1987;328:73–7.

Del Cerro S, Jung M, Lynch G. Benzodiazepines block long-term potentiation in slices of hippocampus and piriform cortex. Neuroscience 1992;49(1):1–6.

Dong J, Montigny C, Blier P. Effect of acute and repeated versus sustained administration of the 5-HT_{1A} receptor agonist ipsapirone: electrophysiological studies in the rat hippocampus and dorsal raphe. Naunyn-Schmiedeberg's Arch Pharmacol 1997;356:303–11.

Duman RS. Novel therapeutic approaches beyond the serotonin receptor. Biol Psychiatry 1998;44(5):324–35.

Evans MS, Viola-McCabe KE. Midazolam inhibits long-term potentiation through modulation of $GABA_A$ receptors. Neuropharmacology 1995;35(3):347–57.

Gerhardt CC, Heerikhuizen H. Functional characteristics of heterologously expressed 5-HT receptors. Eur J Pharmacol 1997;334:1–23.

Godbout R, Chaput Y, Blier P, De Montigny C. Tandospirone and its metabolite, 1-(2-pyramidinyl)-piperazine: I. Effects of acute and long-term administration of tandospirone on serotonin neurotransmission. Neuropharmacology 1991;30:679–90.

Graeff FG, Guimaraes FS, De Andrade TGCS, Deakin JFW. Role of 5-HT in stress, anxiety, and depression. Pharm Biochem Behav 1996;54(1):129–41.

Gulyas GI, Miettinen R, Jacobowitz DM, Freund TF. Calretinin is present in non-pyramidal cells of the rat hippocampus: I. A new type of neuron specifically associated with the mossy fibre system. Neuroscience 1992;48:1–27.

Hart RP, Colenda CC, Hamer RM. Effects of buspirone and alprazolam on the cognitive performance of normal elderly subjects. Am J Psychiatry 1991;148(1):73–7.

Izquierdo I, Da Cunha C, Huang CH, Walz R. Post-training down-regulation of memory consolidation by a GABA-A mechanism in the amygdala modulated by endogenous benzodiazepines. Behav Neural Biol 1990;54:105–9.

Kelso SR, Ganoug AH, Brown TH. Hebbian synapses in the hippocampus. Proc Natl Acid Sci USA 1986;83:5326–30.

Lawlor BA, Hill JL, Radcliffe JL, Minichiello M, Molchan SE, Sunderland T. A single oral dose challenge of buspirone does not affect memory processes in older volunteers. Biol Psychiatry 1992;32(1):101–3.

Lister RG. The amnesic action of benzodiazepines in man. Neurosci Biobehav Rev 1985;9:87–94.

Lucas JJ, Hen R. New players in the 5-HT receptor field: genes and knockouts. TiPS 1995;16:246–52.

Lucki I, Rickels K, Giesecke MA, Geller A. Differential effects of the anxiolytic drugs, diazepam and buspirone, on memory function. Br J Clin Pharmacol 1987;23(2):207–11.

Manabe T. Two forms of hippocampal long-term depression, the counterpart of long-term potentiation. Neurosci Res 1997;8(3–4):179–93.

Markstein R, Matsumoto M, Kohler C, Togashi H, Yoshioka M, Hoyer D. Pharmacological characterization of 5-HT receptors positively coupled to adenylyl cyclase in the rat hippocampus. Naunyn-Schmiedeberg's Arch Pharmacol 1999;359:454–9.

Mori K, Yoshioka M, Suda N, Togashi H, Matsumoto M, Ueno K, Saito H. An incomplete cerebral ischemia produced a delayed dysfunction in the rat hippocampal system. Brain Res 1998;795:221–6.

New JS. The discovery and development of buspirone: a new approach to the treatment of anxiety. Med Res Rev 1990;10:283–326.

Parks CH, Robinson PS, Sibille E, Shenk T, Toth M. Increase anxiety of

mice lacking serotonin 1A receptor. Proc Natl Acad Sci USA 1998; 95:10734–9.

Ramboz S, Oosting R, Amara DA, Kung HF, Blier P, Mendelsohn M, Mann D, Brunner D, Hen R. Serotonin receptor 1A knockout: an animal model of anxiety-related disorder. Proc Natl Acad Sci USA 1998; 95: 14476–81.

Sarter M, McGaughty J, Holley LA, Dudchenko P. Behavioral facilitation and cognition enhancement. In: Sarter M, Nutt DJ, Lister RG, editors. Benzodiazepine receptor inverse agonists. New York: Wiley-Liss, 1995. pp. 213–42.

Schmitz D, Empson RM, Heinemann U. Serotonin reduces inhibition via 5-HT_{1A} receptors in area CA1 of rat hippocampal slices in vitro. J Neurosci 1995;15(11):7217–25.

Seabrook GR, Easter A, Dawson GR, Bowery BJ. Modulation of long-term potentiation in CA1 region of mouse hippocampal brain slices by GA-BA_A receptor benzodiazepine site ligands. Neuropharmacology 1997;36(6):823–30.

Steward O. Topographic origination of the projections from the entorhinal area to the hippocampal formation of the rat. J Comp Neurol 1976; 167:285–314.

Swanson-Park JL, Coussens CM, Manson-Parker SE, Raymond CR, Hargreavens EL, Dragunow M, Cohen AS, Abraham WC. A double dissociation within the hippocampus of dopamine D1/D5 receptor and β-adrenergic receptor contributions to the persistence of long-term potentiation. Neuroscience 1999;92(2):485–97.

Tunnicliff G. Molecular basis of buspirone's anxiolytic action. Pharmacol Toxicol 1991;69:149–56.

Venault P, Chapouthier G, Prado de Carvalho L, Simiand J, Morre M, Dodd RH, Rossier J. Benzodiazepine impairs and *b*-carboline enhances performance in learning and memory tasks. Nature 1986;321: 864–6.

Zalutsky RA, Nicoll RA. Comparison of two forms of long-term potentiation in single hippocampal neurons. Science 1990;248:1619–24.