

Short Report

## Block of 5-HT<sub>2</sub> Receptors Enhances Hippocampal Long-Term Potentiation

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### ABSTRACT

The effect of endogenous serotonin on long-term potentiating (LTP) in region CA<sub>1</sub> was studied by blocking 5-HT<sub>2</sub> receptors with ketanserin in rat hippocampal slices. Such a block significantly enhanced long-term potentiation of the CA<sub>1</sub> population spike induced by high frequency stimulation of the schaffer collateral/ commissural pathway. This implies that serotonin acts on 5-HT<sub>2</sub> receptors in CA<sub>1</sub> to repress long-term potentiation. *Iran. Biomed. J. 2: 129-131, 1998*

*Keywords:* Long-term potentiation; Synaptic plasticity; Serotonin; Hippocampus.

### INTRODUCTION

Extracellular recording techniques in the CA<sub>1</sub> region of the rat hippocampus is used for showing the effects of different drugs on LTP [1]. Long-term potentiation is a form of synaptic plasticity that is widely thought to underlie the formation of memory traces in the brain [2-3]. Essentially, it is a long-lasting increase in the efficacy of synaptic transmission, caused by a brief burst of high frequency, high intensity "conditioning" stimulating to the synaptic pathway under consideration [2]. LTP occurs in many regions of the central nervous system but has received particular study in the CA<sub>1</sub> region of the hippocampus, where the glutamatergic schaffer collateral/ commissural pathway can be potentiated through activation of the N-methyl D-aspartate (NMDA) type of glutamate receptor by a conditioning burst of stimuli [4].

The hippocampal CA<sub>1</sub> region receives many serotonin (5-HT)-containing fibers from the nucleus raphe of brain stem and some of these will presumably be activated by LTP conditioning stimulation. Finally, 5-HT appear to have a dual effect on LTP in the hippocampus as this neurotransmitter was shown to block and facilitate LTP in the Ammon's horn and dentate gyrus respectively [5]. The

aim of this study was to elucidate the effect on LTP of CA<sub>1</sub> serotonergic pathways acting through the 5-HT<sub>2</sub> receptor.

### MATERIALS AND METHODS

Male Wistar rats (200g) were decapitated and the brain was removed into cold oxygenated artificial cerebrospinal fluid (ACSF) of composition NaCl 124 mM, KCl 3 mM, Na<sub>2</sub>HPO<sub>4</sub> 1.25 mM, glucose 10 mM, CaCl<sub>2</sub> 2 mM and bubbled with 95% O<sub>2</sub> and 5% CO<sub>2</sub>. The hippocampus was dissected and transverse slices were cut nominally 400 μm thick using a tissue chopper.

The slices were incubated on a net immersed in oxygenated ACSF for at least an hour, then transferred to submerged slice recording chamber maintained at 28-32°C and superfused with ACSF containing 10 μM bicuculline methiodide and 4 mM MgCl<sub>2</sub>, with or without 10 μM ketanserin (a 5-HT<sub>2</sub> antagonist). Bicuculline methiodide and ketanserin tartrate were obtained from Research Biochemicals Inc. Field potentials were recorded from the cell body layer of the CA<sub>1</sub> region using glass microelectrodes filled with ACSF and having a resistance of approximately 5 megohms (MΩ). Stimulation was

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applied via a bipolar tungsten electrode in the Schaffer collateral/commissural pathway. Test stimulation pulses 0.1 ms negative, of a current which caused population spikes of approximately half maximal amplitude were delivered every 20 sec during the experiment (except during conditioning). Conditioning bursts of stimulation consisted of 6 bursts of pulses of approximately 50% greater intensity than the test pulses, delivered at 10 sec intervals. Each burst consisted of 50 pulses at 100 Hz field potentials were digitized at 10 KHz and stored on a PC cologne for off-line analysis. A peak picking program was used to determine the amplitude of each population spike and results from different experiments were averaged using spreadsheet VP Planner.

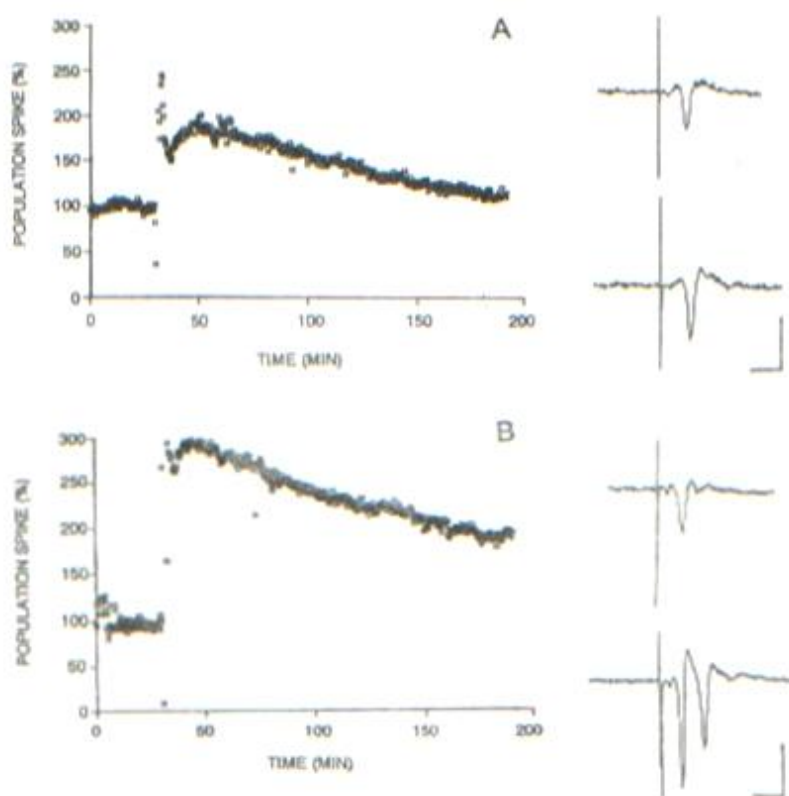
## RESULTS AND DISCUSSION

Results are shown in Figure 1. It can be seen that preincubation of slices in 10 $\mu$ M ketanserin to block 5-

HT<sub>2</sub> receptors caused a potentiation of long-term potentiation. This implies that serotonin is normally released in hippocampal slices in response to test and / or conditioning stimulation and acts via 5-HT<sub>2</sub> receptor to repress LTP of the population spike. The serotonergic innervation of the hippocampus arises from 5-HT neurons of the median and dorsal raphe area [5].

Serotonin mediates several actions on CA<sub>1</sub> pyramidal cells through different 5-HT receptors. Hyperpolarization through 5-HT<sub>1A</sub> receptors in the dendrites [5-7]. Slow excitatory responses (depolarization and reduction in the calcium-activated potassium mediated after hyperpolarization) through 5-HT<sub>4</sub> receptors [5-8] and 5-HT<sub>3</sub> [9]. There is also an outward current (which would produce a hyperpolarization in a non-voltage clamped cell) through 5-HT<sub>2</sub> receptors on the cell bodies [10].

According to the above observation, the effect of ondansetron, a potent and selective antagonist of the 5-HT<sub>3</sub> receptors, significantly increased the magnitude and duration of LTP [9]. The blockade 5-HT<sub>2</sub> receptors



**Fig. 1.** Effect of 5-HT<sub>2</sub> blocker on long term potentiation in CA<sub>1</sub>. Graphs show mean values from 7 (A) and 5 (B) experiments. In each individual population spikes amplitude have been normalized as a percentage of the mean population spike amplitude for the baseline (before conditioning) period for that experiment. Conditioning stimulate was applied at 30 min after the start of each experiment as described in the text. Graph A shows results from control slices. In (B), the slices were incubated in 10 $\mu$ M ketanserin for 30 to 60 min before the start of the experiment and throughout the experimental period. The pairs of field potential traces show means of 10 consecutive field potentials taken 15 min (upper trace) and 60 min (lower trace) after the start of representative experiments from control and ketanserin groups. Bars represent 2 mV, 10 ms.

prevented LTP induction in most, but not all, of the cells [11]. The blockade of LTP by 5-HT could also involve a hyperpolarization of pyramidal neurons through 5-HT<sub>1A</sub> receptors as this effect is blocked by methysergide or spiperone and mimicked by 5-CT (5-carboxyamido tryptamine) [5-13]. With regard to LTP, depletion of serotonin has been reported to inhibit LTP in the dentate gyrus of the hippocampus [12-14] but to have no effect on LTP in CA<sub>1</sub> [14]. Conversely, application of serotonin did not affect the magnitude of LTP produced by high frequency stimulation in CA<sub>1</sub>, either, although it blocked LTP induced by primed burst stimulation [15].

The lack of effect of either depleting or adding serotonin on LTP induced by conditioning stimulation in CA<sub>1</sub> may well be due to the canceling out of the opposing effects exerted by serotonin through the different receptor types. Our results implies that endogenous serotonin acts through 5-HT<sub>2</sub> receptors to depress significantly the long-term potentiation of the population spike induced by high frequency stimulation. Thus blockade of 5-HT<sub>2</sub> receptors enhances long-term potentiation.

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