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BRAIN RESEARCH

Research Report

Long-term depression in the superior cervical ganglion of the rat

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ABSTRACT

Long-term depression (LTD) is a use-dependent decrease in synaptic efficacy widely recognized as a form of synaptic plasticity related to cognitive function in the central nervous system. Such response has previously not been demonstrated in autonomic ganglia. In the isolated superior cervical ganglion (SCG) of the rat (superfused with Locke solution containing 100 μM choline), low-frequency stimulation (LFS, 3–5 Hz/15 min) of the preganglionic nerve produced a long-lasting (up to 3 h), significant (20–40%) decrease in the amplitude of the extracellularly recorded postganglionic compound action potential. Pretreatment of ganglia with the 5-HT_3 receptor antagonist tropisetron (0.5 μM) completely prevented the induction of ganglionic LTD (gLTD). Treatment of ganglia with the 5-HT_3 receptor antagonist MDL 72222 (0.5 μM) during the maintenance phase of established gLTD (1 h after LFS) antagonized the LFS-induced depression. Inhibition of nitric oxide (NO) synthase with L-NOARG (20–50 μM), applied before or after LFS, failed to affect the expression of gLTD. Additionally, pretreatment with the protein synthesis inhibitor emetine (1 μM) totally prevented the expression of gLTD. However, inhibition of protein phosphatase with cantharidin (30 μM) did not interfere with the expression of gLTD. These results indicate the presence of LTD in the rat SCG and suggest that expression of gLTD involves activation of 5-HT_3 receptor.

1. Introduction

Long-term depression (LTD), a form of synaptic plasticity, is an activity-dependent weakening of synaptic strength widely reported and characterized in many regions of the brain. However, the physiological relationship between the much more extensively studied long-term potentiation (LTP) and LTD is not fully understood.

LTD has been induced, by various induction protocols, in many parts of the brain that are known to also express LTP (e.g. CA1 region). In early studies, LTD could be induced by low-frequency stimulation in hippocampal slices of young animals only (Fujii et al., 1991; Dudek and Bear, 1992; O'Dell and Kandel 1994). Later, it has been demonstrated that LTD can also be induced in anesthetized or freely moving adult animals using paired pulse stimulation (Doyere et al., 1996; Thiels et al., 1996; Aleisa et al., 2006).

In the hippocampus, LTP is widely accepted as a cellular model for learning and memory, whereas LTD is thought to work as a "fine-tuner" for cognitive processes (Bear and Abraham, 1996; Kauderer and Kandel, 2000). The dynamic range of LTP and LTD is linked by a modification threshold (θm), which is a function of the postsynaptic response that determines the direction of change in synaptic efficacy (Kim

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and Yoon, 1998). Therefore, if the postsynaptic response to stimulation is above θm, it will induce LTP, but if the postsynaptic response is below θm, LTD will result (Bienenstock et al., 1982; Alzoubi et al., 2008). The development of LTP and LTD depends on the relative activity of kinases (mainly CaMKII and PKC) and phosphatases (mainly calcineurin). The relative activity of kinases and phosphatases in turn depends on the magnitude of the rise in intraterminal calcium concentration. Low to moderate increases in calcium levels activate primarily phosphatases, while greater increases in calcium levels activate mainly kinases (Neveu and Zucker, 1996; Kim and Yoon, 1998). When both enzymes are present, and kinase activity predominates, LTP is expressed, when phosphatase activity predominates, LTD results (Kim and Yoon, 1998).

No published report is available regarding activity-dependent LTD in autonomic ganglia. However, drug induced long-lasting depression of ganglionic transmission has been reported. In the cat sympathetic superior cervical ganglion (SCG) exposure to the opioid peptide, met-enkephalin, produces long-lasting depression of transmission through the nicotinic pathway that is blocked by naloxone or phorbol esters or by high frequency stimulation (HFS) of preganglionic nerve (Zhang et al., 1996). The depressant effect of either prolonged stimulation (40 Hz for 20 min) or phorbol esters is prevented by the protein kinase C (PKC) inhibitor H-7, but not by the calmodulin inhibitor, W-7 or PKA inhibitor, HA 1004, indicating the involvement of PKC in this form of LTD (Zhang et al., 1996). In addition, the expression of this LTD is calcium dependent and not affected by protein synthesis inhibitors (Zhang et al., 1996). Additionally, expression of this response is independent of acetylcholine since it can be evoked during complete blockade of muscarinic and nicotinic ganglionic transmission.

Presently, we report a unique, activity-dependent form of LTD in the SCG of the rat. This ganglionic LTD (gLTD) requires both low-frequency stimulation (LFS) of the preganglionic nerve and the presence of serotonin.

2. Results

2.1. *gLTD is expressed by low-frequency stimulation (LFS)*

Low-frequency stimulation at 3 Hz or 5 Hz for 15 min induced the expression of a long-term depression of ganglionic transmission. The magnitude of gLTD is generally 20–40% below the baseline response ($p < 0.05$, paired *t*-test). Similar magnitudes of gLTD were obtained with either frequencies of 3 Hz or 5 Hz (Figs. 1A and B). The response remained steady with little or no decrement for up to 3 h at 32 °C.

2.2. *Is nitric oxide involved in the expression of gLTD?*

Based on the well-characterized involvement of nitric oxide (NO) in the expression of ganglionic long-term potentiation (gLTP), which indicates that NO is required for the maintenance phase of the response (Alkadhi and Altememi, 1997; Altememi and Alkadhi, 1999; Alkadhi et al., 2001a,b), we studied the possible involvement of NO in the expression of gLTD.

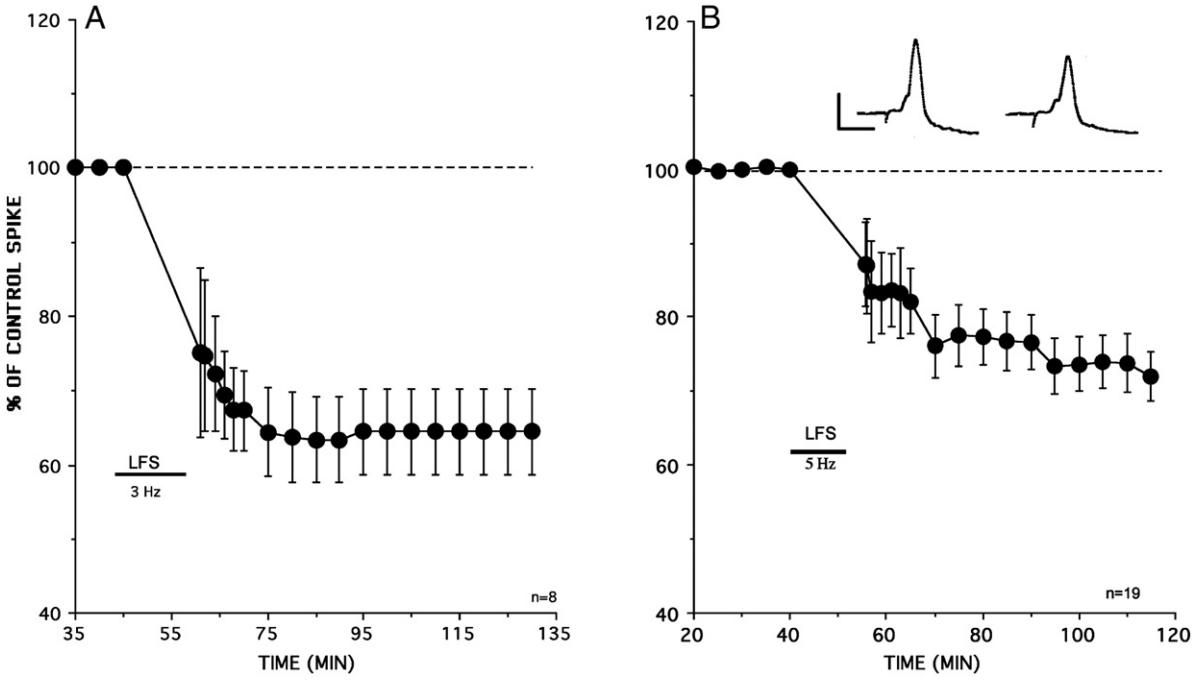

Fig. 1 – Long-term depression of ganglionic transmission (gLTD) is induced in the superior cervical ganglia (SCG) of rat by a volley of low-frequency stimulation (LFS) pulses (supramaximal, 0.3 ms duration) at 3 Hz (A) or 5 Hz (B) for 15 min. Inset in B are the compound action potentials recorded before and after application of LFS; calibration bars (0.5 mV/20 ms) apply to both traces. Each point is the mean ± SEM from 8 ganglia in A and 19 ganglia in B. All points after end of LFS in A and B are significantly different ($p < 0.05$, paired *t*-test) form baseline values.