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Review

Long-term potentiation in mammalian autonomic ganglia: An inclusive proposal of a calcium-dependent, trans-synaptic process☆

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ABSTRACT

Ganglionic synapses have the capability to express long-term potentiation (gLTP) after application of a brief high-frequency stimulus. It has been suggested a possible role of gLTP in some cardiovascular diseases. Although a number of characteristics of gLTP have been described, the precise locations and mechanisms underlying gLTP are not completely known. Current findings support two major conflicting presynaptic and postsynaptic hypotheses. The presynaptic hypothesis posits a presynaptic increase in acetylcholine (ACh) release, whereas the postsynaptic hypothesis proposes a long-lasting enhancement of the nicotinic response on the postsynaptic membrane. An alternative trans-synaptic hypothesis proposes the presynaptic release of a cotransmitter from large dense core vesicles, which postsynaptically enhances synaptic efficacy and accounts for gLTP. Here, we review the studies of LTP, with emphasis on gLTP in mammals, and we examine the findings that support the presynaptic, the postsynaptic and the trans-synaptic hypotheses. We then review our data on the contribution of calcium to gLTP as an approach to elucidate the mechanisms of gLTP. Data on the contribution of calcium to gLTP and on prolonged high-frequency stimulus-dependent fading of LTP have led us to support the trans-synaptic process as responsible for gLTP. Finally, we present a formal working model for the mechanisms of gLTP.

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1. Introduction

A brief train of high-frequency presynaptic stimulation induces a prolonged enhancement in the efficacy of synapses. This phenomenon, known as long-term potentiation (LTP), was first described in the glutamatergic synapses of the rabbit hippocampus (Bliss and Gardner-Medwin, 1973; Bliss and Lömo, 1973). Hippocampal LTP has acquired much attention for its potential role in the cellular mechanisms of learning and memory (Bliss and Collingridge, 1993). Subsequently, a similar phenomenon of

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strengthened synaptic transmission was found in other vertebrate synapses, including peripheral synapses (Brown and McAfee, 1982; Dolphin, 1985; Kuba and Kumamoto, 1990). The first report of synaptic potentiation of ganglionic transmission appeared before the first formal report of hippocampal LTP. Dunant and Dolivo (1968) described a long-lasting increase in ganglionic transmission in the rat superior cervical ganglia (scg) resulting from a brief preganglionic tetanus. This potentiation of transmission in the rat scg was again observed and analyzed in more detail by Brown and McAfee (1982), who referred to this potentiation as LTP because of its similarity with hippocampal LTP. Equivalent phenomena were later demonstrated in other autonomic ganglia in different species using *in situ* (Alonso-deFlorida et al., 1991; Bachoo and Polosa, 1991; Morales et al., 1994) or *in vitro* preparations (Koyano et al., 1985; Scott and Bennett, 1993). Furthermore, muscarinic (Libet and Mochida, 1988) and non-cholinergic (Ashe and Libet, 1981) ganglionic LTP have also been demonstrated. Other forms of potentiation of ganglionic transmission have been described, such as the potentiation induced by the administration of adrenergic agonists (Brown and Dunn, 1983; Kuba et al., 1981) or by the exposition to specific antigens (Weinreich et al., 1995). High-frequency preganglionic stimulation also induces a type of potentiation known as rebound acetylcholine (ACh) (Collier et al., 1983).

It is known that ganglionic synaptic transmission involves sequential changes in membrane potential. It initiates with a nicotinic depolarization responsible of a fast excitatory postsynaptic potential followed by a muscarinic hyperpolarization that gives rise to an inhibitory postsynaptic potential. Then, a late muscarinic depolarization produces a slow excitatory potential, and finally a non-cholinergic depolarization, likely peptidergic, results in a late slow excitatory postsynaptic potential (Karczmar et al., 1986; Nishi and Koketsu, 1968). This review focuses on LTP of nicotinic transmission, mainly in mammalian ganglia.

2. Physiological relevance of gLTP

Like implications of hippocampal LTP in functions such as learning and memory (Bliss and Collingridge, 1993) it is possible that gLTP may play a role in the modulation of peripheral autonomic nervous system activity. It is expected that gLTP enhances tonic efferent impulses to targets, which would modify normal function of diverse organs, including heart, blood vessels and glands. Although the most efficient stimulus frequency to induce gLTP is over 20 Hz, it is possible to induce gLTP with lower frequencies ranging from 5 to 8 Hz (Briggs and McAfee, 1988), which certainly are within the range of spontaneous activity of sympathetic neurons (Jänig et al., 1983; Polosa, 1968). Sympathetic preganglionic neurons (SPN) that usually fire at 5 Hz, can increase their firing rate to bursts of 20 Hz for 1 s in response to an increase in end-tidal CO_2 (Preiss and Polosa, 1977). Therefore, it is reasonable to expect that gLTP may be present *in vivo* in sympathetic ganglia under stress conditions, such as hypercapnia.

Evidence associating expression of gLTP to the development or aggravation of hypertension in animal models have also been presented (Alkadhi et al., 2001b; Gerges et al., 2002). These evidence suggest that most of the neurogenic forms of hypertension are originated and sustained by an increase in the sympathetic-adrenal tone (Guyenet, 2006), which gives rise to elevated plasma levels of norepinephrine and larger electrical activity in the sympathetic efferent nerves (Mancia et al., 1999). It is likely that pathologically enhanced activity of the sympathetic outflow reaching sympathetic ganglia would produce a gLTP *in vivo* (Alkadhi and Alzoubi, 2007). Then, the presence of sustained gLTP in sympathetic ganglia *in vivo* could reinforce the postganglionic outflow to all target organs including blood vessels. This persistent larger efferent activity in blood vessels would increase peripheral vessels resistance leading to elevated blood pressure. In another form of hypertension, elicited by ouabain, it has been shown that the increase in sympathetic nerve activity is associated to the prolongation of gLTP (Aileru et al., 2001). Considering the link between gLTP and hypertension, this plastic phenomenon could be used as a bioassay to monitor installation of hypertension in animal models, such as spontaneous hypertensive rats. It has also been shown that there is a selective age-dependent decline in the capacity for sympathetic ganglia to generate long-term changes in synaptic efficacy (Alzoubi et al., 2010; Wu et al., 1991).

3. Mechanisms underlying ganglionic LTP

The diverse reports addressing the mechanisms underlying gLTP clearly indicate that this phenomenon results from a complex set of events involving enzymes, co-transmitters and second messengers arising from both presynaptic and postsynaptic locations (Alkadhi et al., 1996; Bachoo et al., 1992a; Briggs et al., 1985a; Gonzalez-Burgos et al., 1995; Heppner and Fiekers, 2003; Hogan et al., 1998; Southam et al., 1996). Recently, we have reported that neurotrophins likely participate in gLTP (Arias et al., 2011). Despite all these efforts, the differential contribution of presynapsis and postsynapsis has not been completely defined. In fact, from experiments in mammalian scg, two conflicting hypotheses have been proposed: (i) a presynaptic mechanism that postulates an increase in evoked ACh release as a result of presynaptic Ca^{2+} accumulation, triggered by high-frequency stimulation (Briggs et al., 1985a,b; Briggs and McAfee, 1988; Brown and McAfee, 1982), and (ii) a postsynaptic hypothesis, which states that postsynaptic nicotinic receptors increase in number, affinity for ACh, or ionic conductance by a phosphorylation-mediated mechanism (Collier, 1996; Morales et al., 1994).

4. Presynaptic mechanisms of gLTP

In their pioneer study, McAfee's group first proposed that the presynapsis is the locus of gLTP. In a simple schema, they stated that tetanic stimulation increases $[Ca^{2+}]$ in the preganglionic terminals, leading to a larger release of ACh that is responsible for gLTP (Brown and McAfee, 1982). The presynaptic hypothesis was also based on a collection of findings described in a series of further articles (Briggs et al., 1985a,b; Briggs and McAfee, 1988; reviewed in McAfee et al., 1987; Briggs, 1995): (1) potentiation was elicited by preganglionic tetanic stimulation, but not by antidromic postganglionic stimulation (Brown and McAfee, 1982), (2) potentiation was not induced by non-synaptic stimulation (intracellular depolarization) of individual postganglionic neurons (Briggs and McAfee, 1988), and (3) release of endogenous ACh into the bath medium was enhanced in parallel with synaptic transmission after tetanic stimulation (Briggs et al., 1985b).

Briggs et al. (1985a) were interested in knowing whether activating nicotinic receptors during the conditioning tetanus is important for the expression of gLTP. They found that gLTP induction did not depend on the release of ACh during the train because carbachol, a cholinergic agonist, was unable to mimic tetanic stimulation in producing gLTP. Furthermore, the use of selective nicotinic or muscarinic antagonists during the train did not affect gLTP. In the same work these authors explored whether neurotransmitters besides ACh could induce gLTP. They found that α- and β-adrenergic antagonists applied during the train did not affect gLTP (Briggs et al., 1985a). To further rule out the involvement of a chemical mediator released during the train, Briggs et al. (1985a) explored whether potentiation can be heterosynaptically elicited, *i.e.* induced by the application of a tetanizing train to