PLASTICITY OF GABAERGIC SYNAPTIC TRANSMISSION

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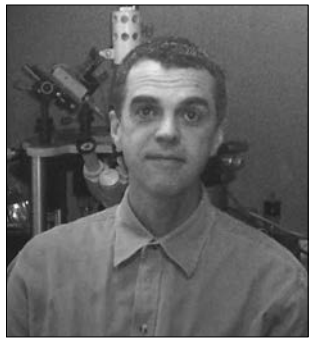

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Modulation and short-term plasticity of GABAergic synaptic transmission

The suppressing effect of acetylcholine on GABAergic synaptic transmission mediated by presynaptic mechanisms has been well documented. According to our results (Storozhuk et al., 2001), postsynaptic mechanisms also substantially contribute to the modulatory effect of acetylcholine on GABAergic synaptic transmission, however, in a fraction of GABAergic connections in hippocampal cell cultures. Involvement of postsynaptic mechanisms in the modulatory effect of acetylcholine has been also reported more recently on hippocampal slices (Zhang and Berg, 2007). It is likely that the postsynaptic component of acetylcholine modulatory effect on GABAergic synaptic transmission is rather a general phenomenon, since modulation of currents evoked by exogenous GABA application was also observed in chick cilliary neurons.

Short-term plasticity of GABAergic synaptic transmission evoked by tetanic stimulation

We have found that in distinct pairs of neurons the same tetanic stimulation (30 Hz, 4 s) evokes either posttetanic potentiation (PTP) or posttetanic depresssion (PTD). This differential effect was observed in hippocampal (Storozhuk et al., 2002) and neocortical cell cultures (Storozhuk et al., 2005a). Since presynaptic mechanisms contribute to both PTP and PTD, we hypothesized that the differential effect of the tetanic stimulation is due to heterogenety of presynaptic neurons. To test this idea, we compared several properties of the connections belonging to the PTP and PTD groups. We have found that, on average, evoked IPSCs in the connections facilitated by the tetanization have smaller amplitudes and larger coefficients of variation (CV) of IPSC amplitude compared to the connections depressed by the tetanization. We also estimated quantal parameters for both groups assuming that transmitter release is reasonably described by a simple binomial distribution. We established that the background release probability (P) is substantially lower in the connections facilitated by tetanization ($P \sim 0.5$) than in the depressed connections ($P \sim 0.9$). and suggest that this difference may underlie the differential effect of the tetanization. We have also found that the tetanization induces opposite effects on connections made by distinct presynaptic neurons with the same postsynaptic cell (convergent connections) in the fraction of postsynaptic neurons studied. These results also support the idea that properties of the presynaptic neuron are of primary importance for the observed differential effect of tetanization. Crucial importance of the processes occurring in the presynaptic neuron for PTP of GABAergic transmission, in particular that of basal probability of release, Ca^{2+} buffering (Jensen et al., 1999a), entry of Ca^{2+} through L-type calcium channels have been previously demonstrated (Jensen et al., 1999b).

Moreover, PTP was turned in PTD in basket cell granular cell synapses in slices (Jensen and Mody, 2001), which suggests that differential expression of L-type calcium channels may be a cause for differential effect of the tetanization observed in our experiments. While contribution of this factor is quite likely to occur, this is probably not the only reason since we did not observe transformation of PTP to PTD in spite of the pronounced effect of nifedipine on PTP. The difference in probability observed in our experiments, in particular, may be due to differences in tonic activation of PTD connections and/or tonic inhibition of PTP connections. Although much of the variability in the basal probability of release is thought to arise from intrinsic properties of different classes of synapses, it has been recently demonstrated that unique properties of mossy fiber synapses are due to low probability of transmitter release which results from tonic action of extracellular adenozineadenosine acting on presyanaptic A1 receptors (Moore et al., 2003). It may be also suggested that the observed difference in probability of transmitter release somehow correlates with differential expression of calcium binding proteins in the GABAergic neurons. Indeed, diversity of interneurons in terms of expression of calcium binding proteins has been well documented (Freund and Buzsaki, 1996). A crucial role of parvalbumin (Vreugdenhil et al., 2003) and calbinding (Blatow et al., 2003) in use-dependent plasticity of GABAergic transmission has been recently demonstrated as well. Therefore, it seems to be an important issue for future studies to identify immunocytochemically presynaptic neurons with low and high probability of transmitter release.

It has been shown previously that mitochondria are of crucial importance *for* PTP at crayfish neuromuscular junction (Tang and Zucker, 1997). More recently, evidence indicating involvement of mitochondria in PTP at mammalian neuromuscular junction (David and Barrett, 2003) and in regulation of presynaptic calcium at the central glutamatergic terminals (Billups and Forsythe, 2002) has been reported.

However, lack of evidence for mitochondrial involvement in PTP at other synapses as well as for substantial differences between synapses raised several questions, in particular, whether mitochondria are involved in PTP at the central inhibitory synapses? We found that, indeed, mitochondria are involved in PTP at neocortical GABArgic synapses (Storozhuk et al., 2005a). Thus, involvement of mitochondria in this form of plasticity may be essential for many types of synapses.

Short-term plasticity of GABAergic synaptic transmission evoked by depolarization of postsynaptic neurons

Heterogeneity of GABAergic synapses can be also revealed by activation of postsynaptic neurons. Indeed, brief depolarization of postsynaptic neurons in hip-

pocampus and cerebellum results in a transient depression of GABAergic inhibitory input, called "depolarization-induced suppression of inhibition" (DSI), phenomenon observed only in a fraction of synaptic connections (Ohno-Shosaku et al., 1998). We studied whether DSI is present in the rat neocortical networks (Storozhuk et al., 2005b). We found that the depolarization of postsynaptic neurons evokes suppression of IPSC amplitude in 6 out of 26 neuronal pairs tested which lasted for ~70 sec. The suppression of IPSC amplitude was accompanied by changes of paired-pulse ratio and IPSC coefficient of variation (CV), indicating involvement of a presynaptic mechanism in this phenomenon. Thus, our results are in agreement with previous observations in hippocampal and cerebellar synapses.

Homeostatic plasticity of GABAergic synaptic transmission

Cellular homeostasis is one of the most basic processes by which cells responds to a change in the intracellular or extracellular environment and maintains a constant physiology (Davis and Bezprozvanny, 2001). Many years ago, it was postulated that homeostatic mechanisms maintain an environment in which the brain can function normally, independently of fluctuations in the external environment (Cannon, 1937). More recently, it has become apparent that neural activity itself is subject to homeostatic regulation and this prevents neural circuits from becoming hyper- or hypoactive (Turrigiano and Nelson, 2004). It has been proposed to consider plasticity in neuronal network as occurring in two forms (Turrigiano, 1999; Turrigiano and Nelson, 2000): use-dependent plasticity which modifies the network properties, and homeostatic plasticity which to some extent counteract use-dependent changes. Without stabilizing mechanisms operating at the level of neural circuits, activity-dependent forms of plasticity such as long-term potentiation (LTP) and long-term depression (LTD) can drive neural activity towards runaway excitation or quiescence (Turrigiano and Nelson, 2004). In this regard, we studied effects of prolonged decrease (using sodium channel blocker TTX) and increase (using GABAA receptor antagonist bicuculine) of neuronal firing on GABAergic synaptic transmission.

It has been shown previously that prolonged block of neuronal activity results in decreasing synaptic inhibition in visual cortex (Kilman et al., 2002) and spinal cord neuronal networks (Galante et al., 2000). Our results indicate that similar changes also occur in hippocampal cell cultures. Indeed, we have shown that TTX-pretreatment decreases the amplitude of evoked IPSCs, decreasing thus the amount of inhibition in this neuronal network. A decrease of GABAergic transmission efficacy may occur, in particular, due to some postsynaptic changes, for instance as a result of decreased number of postsynaptic receptors or changes of GABAA-receptors properties (Macdonald and Olsen, 1994)

(Sieghart, 1995) (Cherubini and Conti, 2001). In our experiments, the decrease of IPSC amplitude induced by TTX pretreatment was accompanied by a pronounced increase in the IPSC cofficient of variation. Thus, our results suggest that changes of IPSC amplitude are at least in part due to a presynaptic mechanism. This suggestion can be supported by the results obtained earlier in cultured visual cortex neurons (Kilman et al., 2002). Indeed, with using immunocytochemical approach, it has been demonstrated that TTX treatment decreases staining for GAD65, the presynaptically localized isoform of the synthesis enzyme for GABA. This in turn suggests a decrease of GABA syntesis and perhaps a decrease of GABAergic synapse number. Further investigation is required to determine exact origin of this change. On the other hand, we cannot exclude a possibility that postsynaptic changes also contribute to induced by to TTX pretreatment decrease of GABAergic transmission efficacy in our experiments as it was observed in visual cortex neurons. In fact, TTX-treatment in the latter preparation decreased the amplitude of miniature GABAergic IPSCs and this effect was accompanied by a decreased number of postsynaptic reseptors (Kilman et al., 2002).

Therefore, a question of postsynaptic changes involvement in homeostatic regulation of GABAergic transmission should be further studied. In this regard, it is worth to mention our recent results concerning homeostatic changes of GABAergic transmission evoked by prolonged exposure to bicuculline in hippocampal cultures (Ivanova and Kostyuk, 2004). According to our results, acutely applied bicuculline and TTX produce opposite effects on neuronal firing in hippocampal cell cultures. Prolonged treatments with these drugs induce opposite changes of GABAergic synaptic efficacy. However, while bicuculline pretreatment drammatically increased evoked IPSC amplitude, it did not affect either IPSC coefficient of variation or paired pulse depression (Ivanova and Kostyuk, 2004). Thus, generally, both pre- and postsynaptic mechanism are likely to be involved in homeostatic regulation of GABAergic transmission in hippocampal networks.

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