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Review

Presynaptic, extrasynaptic and axonal $GABA_A$ receptors in the CNS: where and why?

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Abstract

Although $GABA_A$ receptors are widely distributed at inhibitory synapses on dendrites and cell bodies of neurons, they also occur in other places, in particular at synapses made on axons and in extrasynaptic membranes. This review summarises some of the evidence that presynaptic receptors modulate transmission not only at primary afferents in the spinal cord, but also at a variety of sites in the brain, including hippocampal mossy fibres. These receptors modulate transmitter release via several different mechanisms. Another form of unconventional $GABA_A$ receptor-mediated signalling is the mediation of a tonic conductance, seen in granule cells of the cerebellum and dentate gyrus and also in hippocampal interneurons. Tonic signalling appears to be mediated by extrasynaptic receptors. The adaptive significance of this form of signalling remains poorly understood.

Keywords: Presynaptic inhibition; GABA receptors; Tonic; Phasic; Subunit

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1. Introduction

$GABA_A$ receptors are widely distributed in the mammalian CNS, where they are conventionally thought to mediate fast synaptic inhibition. The textbook model of inhibition holds that $GABA_A$ receptors at synapses on cell bodies or dendrites open an anion conductance, which results in both postsynaptic hyperpolarisation (mediated by Cl^- influx) and shunting of excitatory currents. This leads to a transient decrease in the probability of initiation of an action potential.

This model may not always be correct because $GABA_A$ receptors can sometimes depolarise neurons, and possibly even have a net excitatory action: the reversal potential of the mixed Cl^-/HCO_3^- conductance is frequently more positive than the resting membrane potential (Cherubini et al., 1991), especially in some immature neurons prior to the expression of the main Cl^- extrusion system, the KCC2 transporter (Rivera et al., 1999). Under some circumstances, $GABA_A$ receptor activation can result in the opening of voltage-gated Ca^{2+} channels, and even in the initiation of action potentials.

Another important question surrounding the role of $GABA_A$ receptors is to what extent they occur at sites other than postsynaptic elements of inhibitory synapses on cell bodies and dendrites. Other locations, such as on presynaptic boutons, extrasynaptic membranes on postsynaptic neurons or even on axons of the white matter, have been demonstrated with a variety of methods. The function and adaptive significance of these receptors remain incompletely understood. This brief review attempts to summarise some of the evidence that such receptors are abundantly expressed in some parts of the CNS, to examine what effects these receptors have on neuronal signalling, and to speculate about their possible adaptive significance.

The broader subject of presynaptic ionotropic receptor function in the CNS has been considered recently by Engelman and MacDermott (2004). The role of tonically active $GABA_A$ receptors has been considered by Semyanov et al. (2004).