EXTRASYNAPTIC $GABA_A$ RECEPTORS: PHYSIOLOGICAL ROLE, PLASTICITY, AND NEW PHARMACOLOGICAL PROSPECTIVES

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$GABA_A$ receptors ($GABA_ARs$) belong to the "cys-loop" superfamily of ligand-gated ion channels and are responsible for the fast component of the inhibitory postsynaptic current. The $GABA_AR$-operated ion channel is primarily permeable to chloride and its activation results in the influx of Cl^- ions into the cell and in the hyperpolarization of the neuronal membrane that causes an increase in the threshold of neuronal excitability. $GABA_ARs$ are the target for a number of clinically important drugs such as benzodiazepines, barbiturates, general anesthetics and steroids. Alterations in the function of $GABA_ARs$ are also implicated in several neurological and psychiatric disorders such as epilepsy and anxiety. Deletion of the GABRB3 gene, which encodes the β_3 subunit, is associated to Angelman syndrome, while mutations in *GABRA1* or *GABRA2* genes are related to specific forms of epilepsy.
New evidence show that the GABAergic inhibition involves both phasic and tonic components. Phasic inhibition is mediated by postsynaptic $GABA_ARs$, composed of $\alpha_n\beta_n\gamma_2$ subunits, that are activated by GABA released into the synaptic cleft, whereas tonic inhibition is mediated by a more continuous activation of $GABA_ARs$, composed of $\alpha_{4/6}\beta_n\delta$ subunits, that are localized extrasynaptically, particularly in the hippocampus, thalamus, and cerebellum. Tonic GABAergic conductance is activated in response to the low concentrations of ambient GABA, and extrasynaptic $GABA_ARs$ are characterized by a higher affinity for GABA and a reduced rate of desensitization. These receptors also are insensitive to benzodiazepine receptor ligands, but possess higher sensitivity to the hypnotic drug THIP, to endogenous neurosteroids such as allopregnanolone and THDOC which are thus regarded as their main physiological modulators, and to ethanol. Extrasynaptic $GABA_AR$ gene expression and function are altered by long-term treatment with ethanol as well as in response to physiological fluctuations in brain levels of neurosteroids such as during the ovarian cycle or during pregnancy. Given the crucial role of extrasynaptic $GABA_ARs$ in regulating neuronal excitability, research on the identification of selective drugs acting on them appears promising for the treatment of different neurological and psychiatric disorders.