

**ELECTROPHYSIOLOGICAL STUDIES ON THE MECHANISMS
DETERMINING THE KINETICS AND PHARMACOLOGICAL
MODULATION OF GABAergic SYNAPTIC TRANSMISSION**

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The time course of GABAergic the inhibitory synaptic currents is a key factor in determining the synaptic signal integration in neurons. The kinetic shape of these currents depends on the amount and time course of neurotransmitter release from the nerve terminal and the kinetics of the postsynaptic GABAA receptors. The synaptic agonist is known to reach millimolar concentrations, and is cleared from the synaptic cleft within hundreds of microseconds. This implies that the postsynaptic receptors are activated under conditions of extreme non-equilibrium. The GABAergic synaptic currents (IPSCs) can be routinely measured in the whole-cell mode of the patch-clamp technique. However, the analysis of the IPSCs is insufficient to characterize the kinetics of postsynaptic receptors. The kinetic properties of ligand-gated channels can be determined by analysing the dose-response relationships for current responses to exogenous agonist applications. However, the perfusion of agonist should be sufficiently fast to mimic the synaptic transient of the neurotransmitter. Using the ultrafast piezoelectric-driven perfusion system, a complete exchange of agonist can be achieved within 100 μ s, thus fulfilling this requirement. The analysis of current responses to ultrafast GABA applications permitted the characterization of the kinetics of these receptors with time resolution adequate to the synaptic events. The application of this technique also made it possible to describe the mechanism of pharmacological modulation of GABAA receptors by several clinically relevant compounds such as benzodiazepines, phenothiazines, and barbiturates as well as by other modulators such as pH, or Zn ions. The native GABAA receptors are known to be extremely heterogeneous. GABAA receptors composed of different subunits show different kinetic and pharmacological properties. For this reason, the expression of recombinant receptors with a strictly defined subunit composition in cell lines provided the means to further characterize the kinetics and pharmacology of the GABAA receptors in strict relation to their tertiary structure.

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