第62回 脳研・高度先進合同セミナー

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Professor Joe-Henry Steinbach

(Dept. of Anesthesiology, Washington University School of Medicine, St. Louis, USA)

Neurosteroid actions on GABA-A receptors: sites and mechanisms

Potentiating neurosteroids increase the strength of neuronal inhibition by enhancing the activity of GABA-A receptors, increasing the response to lower concentrations of GABA and prolonging the synaptic current. Potentiation occurs because neurosteroids reduce the rate at which the open channel closes, while the affinity of the receptor for the neurotransmitter GABA is not changed. Potentiating steroids also enhance the response to allosteric activators of the GABA-A receptor that can open the channel but bind to sites that are different from the GABA-binding site. Overall, the basic mechanism is to affect receptor kinetics rather than receptor affinity for agonists.

Potentiating steroids interact with the 1st membrane-spanning region (TM1) of the α subunit. When a single residue in this region is mutated potentiation by steroids (but not other drugs) can be removed. However, potentiation can be restored to the receptor by mutations that convert the TM1 of the β or γ subunit to the sequence in α. This observation indicates that it is not a unique property of the α subunit, or of the subunits adjacent to the α subunit that allows potentiation. The native α subunit is involved in binding both steroid and GABA itself. However, potentiation does not require that a single subunit bind both drugs since receptors can be constructed that lack one or the other site on selected subunits, and potentiation is preserved. These findings indicate that steroid binding affects the gating properties of the receptor as a whole, rather than changing the function of a single subunit.

どうぞお気軽に御参加下さい。学生の参加も大歓迎です。

Information: 上野伸哉（内5137）、若林孝一（内5130）、伊東健（内5157）