The Sensitivity of GABA-Receptor is Increased by Biogenic Amines

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The sensitivity of nicotinic ACh (acetylcholine) -receptor to its agonist has been recently reported to be depressed or increased by the action of transmitters other than ACh (Akasu et al. 1981a, b; Koketsu et al. 1982b). These experimental observations led to a new concept, namely that, under physiological conditions, the sensitivity of nicotinic ACh-receptor can be modulated by the actions of endogenous substances. The latter could be termed endogenous antagonists or sensitizers (Koketsu, 1984; Koketsu and Akasu, 1985). Furthermore, it was pointed out that the concept of the sensitivity of a membrane receptor being modulated by transmitters may be valid not only in the case of nicotinic ACh-receptor but also in the cases of other receptors (Koketsu, 1984; Koketsu et al. 1982a). That is, in general, the sensitivity of all kinds of receptors to their agonists may be modulated by the actions of many kinds of transmitters, viz. endogenous antagonists or sensitizers.

The present communication reports experimental evidence to support this concept. As will be shown, the sensitivity of GABA (7-aminobutyric acid) -receptor is increased by histamine, 5-HT (5-hydroxytryptamine) and adrenaline. Thus, it would be understood that these biogenic amines may be endogenous sensitizers of the GABA-receptor.

In the present experiment, the effects of biogenic amines (histamine, 5-HT and adrenaline) on the sensitivity of GABA-receptor was tested. The GABA-receptor of bullfrog spinal ganglion cells (Morita et al. 1984) was used as a model of the GABA-receptor. The sensitivity of GABA-receptor was estimated by measuring the membrane potential changes of the spinal ganglion cells induced by direct applications of GABA to a ganglion. The membrane potential changes of spinal ganglion cells was recorded by use of the sucrose-gap method (Nishi and Koketsu, 1968). A lumbar spinal ganglion was carefully isolated together with attached dorsal root and sciatic nerves. An isolated ganglion was rapidly and continuously perfused with Ringer solution. In order to apply histamine, 5-HT and adrenaline to the ganglion, the perfusate was changed for a certain period to a Ringer solution containing each drug of which concentration was controlled. GABA (3 mM) was applied in drop form into the portal of the organ bath from a 18 gauge needle of a 1 ml glass syringe. The composition of Ringer solution is as follows (mM): NaCl 110, KCl 2.0, CaCl2 1.8, NaHCO3 2.4 and glucose 2.5. Cl- free solution was made by a replacement of all Cl ions with glutamate ions. Drugs used in the present experiments are adrenaline bitartrate, histamine hydrochloride, sero-
tonin-creatinine sulphate, picrotoxin, and γ-aminobutyric acid. All drugs were obtained from Wako. All experiments were carried out at room temperature (22–24°C).

Depolarizing responses ranging between 2 and 3 mV (GABA-induced potential) were recorded from individual ganglia when GABA was added to the superfusing solution. Although the amplitude of recorded potential changes varied according to each different preparations, the amplitude of GABA-induced potentials appeared to be fairly constant for more than 3 hours using the drop method of application (Fig. 1a).

GABA-induced potential persisted in a Ca²⁺ free high Mg²⁺ (10.8 mM) solution for more than 60 min. In Cl⁻ free glutamate solution, GABA-induced potential was almost completely blocked. Picrotoxin (100 mM) strongly suppressed the amplitude of GABA-induced potential.

The amplitude of GABA-induced potentials was found to be augmented markedly and reversibly in the presence of his-

![Fig. 1. Effects of biogenic amines on the GABA-induced potentials.](image)

Records a show a consecutive recording of GABA-induced potential produced by application of GABA (3 mM) in drop form into the portal of the organ bath from a 18 gauge needle of a 1 ml glass syringe; one drop of GABA solution was equivalent to 0.022±0.002 ml (n=40). Note that a reproducible GABA-induced potential could be recorded over a few hours using the drop method of application.

Records b, c and d show the effects of histamine (2 mM), 5-HT (2 mM) and adrenaline (2 mM), respectively, on the GABA-induced potentials. Records b and c were obtained from the same ganglion. Record 1 and 2 were obtained before and 10 min after bath application of these biogenic amines. Records 3 were obtained 10 min after withdrawal of these drugs.
amine (1-2 mM). When the external solution was changed from the Ringer solution to a Ringer solution containing histamine (2 mM), no detectable changes were observed in the resting membrane potential. Interestingly, as long as histamine remained in superfusing solution, a marked augmentation of the GABA-induced potential was sustained. The mean augmentation of GABA response was about 40% (n=6). This experimental observation indicated that the sensitivity of GABA-receptor to GABA is increased by the action of histamine.

Similar potentiation of the GABA-induced potential was also observed in the presence of 5-HT (2 mM). When 5-HT was added to the external solution (Ringer solution), the resting membrane potential was slightly depolarized by 1-2 mV. Despite of depolarization of the resting membrane potential in the presence of 5-HT, amplitude of the GABA-induced potential was augmented reversibly. Augmentation of GABA-induced potential was about 35-40%. Fig. 1b, c demonstrates the effects of histamine and 5-HT on the GABA-induced potential recorded, successively, from the same single ganglionic preparation.

Adrenaline (1-2 mM) also produced an augmentation of the amplitude of the GABA-induced potential. An application of adrenaline (2 mM) to the bath caused a slight membrane depolarization (2-3 mM) on spinal ganglion neurones. The GABA-induced potential was increased to more than 145% of the control amplitude. Augmentation of GABA-induced potential disappeared immediately after withdrawal of GABA from superfusing solution (Fig. 1d).

The present experiment demonstrated that the sensitivity of GABA-receptors located at the membrane of spinal ganglion cells is increased in the presence of biogenic amines, histamine, 5-HT and adrenaline. Since the amplitude of GABA-induced potential is determined by the GABA-induced current and resting membrane potential and conductance, the amplitude of GABA-induced current would be the exact index of the GABA-receptor sensitivity. The GABA-induced potential, however, was augmented without appreciable changes in the resting membrane potential in the presence of histamine. It was also augmented despite a depolarization of the resting membrane potential in the presence of 5-HT and also in the presence of adrenaline. These results strongly suggest that the GABA-induced current must have been increased by the actions of histamine, 5-HT and adrenaline. This should be confirmed by using voltage-clamp experiments, in which the GABA-induced current recorded from a single ganglion cell could be analysed.

The mechanism underlying the increase in the GABA-receptor sensitivity induced by histamine and 5-HT is not clarified in the present experiment. Analyses of the GABA-current recorded by voltage-clamp experiment from single cells would shed light on the mechanism.

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References


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