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EFFECT OF γ-AMINOBUTYRIC ACID ON HUMAN JEJUNUM "IN VITRO"

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Peripheral GABA receptors have been found in a variety of tissues of different species. The gut has been the most studied subject, where the presence of GABA neurons within the myenteric plexus has been demonstrated (Jessen et al., 1983). In this structure two pharmacologically distinct GABA receptors are present, that have a modulatory role on the release of neurotransmitters: 1) GABA-A receptors, whose activation leads to an augmentation of the release of Ach and a contraction of the longitudinal muscle strip of guinea pig ileum (Kleinrock and Kilbinger, 1983); in the rat duodenum GABA-A receptors seem to activate the release of an inhibitory purinergic neurotransmitter (Maggi et al., 1984). 2) GABA-B receptors, whose activation determines a reduction of the release of Ach and a relaxation of the electrically stimulated guinea pig ileum (Bowery et al., 1981; Giotti et al., 1983). Until now the effect of GABA on the human gut has not been studied. Therefore we decided to evaluate the action of GABAergic drugs on human jejunum strips.

Longitudinal strips about 1 cm long and 3 mm wide of human jejunum were obtained from surgical interventions for malignant tumors. The strips were set up under a tension of 1 g in an isolated-organ bath and perfused with Krebs solution plus choline at 37°C bubbled with 95% oxygen. The motility of the longitudinal muscle was recorded; the measurement of the effects of the drug was made by the evaluation of the "motility index" (product frequency x amplitude of contractions).

Human jejunum generally exibited an intense spontaneous motility. The administration of GABA (3×10^{-6} - 10^{-4} M) caused a dose-dependent reduction in the amplitude and frequency of

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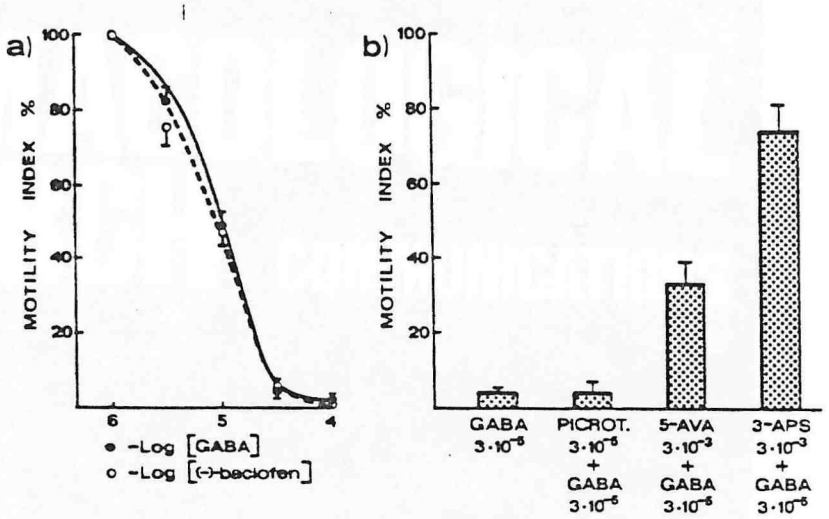

Fig. 1. a) Dose-response curve of GABA and (-)-baclofen; b) influence of 3-APS, 5-AVA and picrotoxin on GABA effect. Motility index is expressed as percentage of values obtained immediately before drug administration.

contractions, and then in the "motility index" ($ED50=10^{-5}$ M) (fig. 1a); this effect was mimicked by the GABA-B agonist (-)-baclofen (fig. 1a), while the GABA-A agonists, homotaurine (3-APS) ($3x10^{-5}$ M) and muscimol ($3x10^{-5}$ M), had no significant effect. The effect of GABA ($3x10^{-5}$ M) was not affected by the GABA-A antagonist picrotoxin (10^{-5} M), but was reduced by the weak GABA-B antagonist 5-aminovaleric acid (5-AVA) ($3x10^{-3}$ M) and almost abolished by the GABA-B antagonist homotaurine ($3x10^{-3}$ M) (fig. 1b). Moreover tetrodotoxin ($3x10^{-7}$ M) prevented the action of GABA.

In conclusion these results demonstrate the inhibitory effect of GABA on the motility of human jejunum "in vitro", mediated by the activation of neuronal GABA-B receptors; we have not observed any effect mediated by GABA-A receptors.

BOWERY, N.G., DOBLE, A., HILL, D.R., HUDSON, A.L., SHOW, J.S. and TURNBULL, M.J. (1981). Eur. J. Pharmac. 71, 53-70.

GIOTTI, A., LUZZI, S., SPAGNESI, S. and ZILLETTI, L. (1983). Br. J. Pharmac. 78, 469-478.

JESSEN, K.R., HILLS, J.M., DENNISON, M.E. and MIRSKY, R. (1983). Neuroscience 10, 1427-1442.

KLEINROCK, A. and KILBINGER, H. (1983). Naunyn-Scmiedebergs Arch. Pharmac. 322, 216-220.

MAGGI, C.A., MANZINI, S. and MELI, A. (1984). J. Auton. Pharmac. 4, 77-85.