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Chronic treatment with otilonium bromide affects the tachykinergic and nitrergic systems in the rat colon

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Otilonium bromide (OB), a quaternary ammonium derivative used for the treatment of intestinal motility disorders such as the irritable bowel syndrome (IBS). It exerts several actions, among which the ability to bind to the neurokin-2 receptor (NK2r) inhibiting NK2r mediated contraction and, in the human colon, NK2r internalization in the smooth muscle cells (SMC) (Cipriani et al., 2011). Substance P (SP) is an excitatory neurotransmitter that, interacting mainly with the neurokinin-1 receptor (NK1r), can stimulate bowel motility by SMC direct activation or inhibit it by an indirect action through enteric neural circuits. In an IBS rat model, the increase in NK1r-mediated colonic motor response was associated to a decrease in the nitrergic activity.

On these basis, we tested whether OB modifies NK1r, NK2r, SP and neuronal nitric oxide synthase (nNOS) expression in rat colon after chronical administration of the drug (2 or 20mg/Kg/daily) for 10 or 30 days. At the end of the treatments, specimens of proximal colon were collected and the expression of NK1r, NK2r, SP and neurogenic and myogenic nNOS were evaluated by immunohistochemistry and Western blot. Our data show that SP expression was significantly decreased in 10 and 30 days treated rats in myenteric ganglia and, in 30 days treated rats, also in the intramuscular nerve fibres. No quantitative change of the two NKr was observed, whereas, after 30 days, the NK1r was concentrated in the SMC cytoplasm. In parallel, the neurogenic nNOS expression increased and reached the significance after 30 days of treatment; the myogenic nNOS expression increased, but these increase reached the significance only at 10 days.

Our findings suggest that the main target of the OB chronically administered is the NO-mediated system that is stimulated earlier at the muscular level, later at the neuronal level. We interpret the systemic decrease in the SP expression as consequence of the potentiated NO availability in the ganglia and muscle coat. If true, the late concentration of NK1r in the cytoplasm could represent an attempt of the SMC to overcome the deficit of its main ligand SP.

Referencees

Cipriani G, et al. (2011). Effect of otilonium bromide and ibodutant on the internalization of the NK(2) receptor in human colon. Neurogastroenterol Motil. 23, 96-102.

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