

Repeated administration of the spasmolytic otilonium bromide counteracts functional and neurotransmitters' changes in the colon of rats underwent to wrap restraint stress

Chiara Traini¹ - Stefano Evangelista² - Vincent Girod³ – Maria Giuliana Vannucchi¹

¹ Department of Experimental and Clinical Medicine, Research Unit of Histology and Embryology, University of Florence, Florence, Italy - ² Menarini Ricerche Spa, Preclinical Development Department, Florence, Italy - ³ Syncrosome, Gastrointestinal Unit, Marseille, France

Otilonium bromide (OB) is a quaternary ammonium derivative successfully used for the treatment of irritable bowel syndrome (IBS). Several *in vitro* experiments in human and rat colon demonstrated its spasmolytic capability due to the block of muscarinic and tachykinin receptors and L-type Ca²⁺ channels. Moreover, *in vivo* OB administrations showed interesting interaction with the enteric nervous system in healthy rats (1). The wrap restraint stress (WRS) is considered an adequate model of psychosocial stressor, able to induce most of the IBS signs and symptoms. WRS leads to important changes in the enteric neurotransmitters of rat colon, as recently demonstrated (2). Consequently, we chose this animal model to investigate whether a repeated, oral treatment with OB prevented the functional and neurotransmitters' changes reported in rats underwent to WRS. The results obtained by using multiple experimental approaches (*in vivo* colonic functional evaluations, routine histology, immunohistochemistry and western blot) showed that OB is able to counteract most of the morphological changes caused by WRS in the colonic wall. In particular, the drug prevents the decrease in SP-, NK1r-, nNOS-, VIP- and S100 β -immunoreactivity (IR) and the increase in CGRP- and CRF1r-IR detected in WRS rats. On the contrary, OB does not interfere with the mild mucosal inflammation and does not affect the increase in CRF2r-immunoreactive neurons observed in WRS rats. Moreover, OB *per se* increases the muscarinic receptor 2 expression in the muscle wall and decreases the number of the myenteric ChAT-immunoreactive neurons. Functional findings show a significantly reduction in the number of spontaneous abdominal contraction in OB treated rats. The ability of OB to block L-type Ca²⁺ channels, also expressed by enteric neurons, might explain the drug efficacy in preventing excessive neuronal response to stress.

This work was supported by grants from Menarini I.F.R.

References

- [1] Traini et al. (2013) Chronic treatment with otilonium bromide induces changes in L-type Ca²⁺ channel, tachykinins, and nitric oxide synthase expression in rat colon muscle coat. *Neurogastroenterol Motil*; 25: e728; doi: 10.1111/nmo.12197.
- [2] Traini et al. (2016) Changes of excitatory and inhibitory neurotransmitters in the colon of rats underwent to the wrap partial restraint stress. *Neurogastroenterol Motil*; doi: 10.1111/nmo.12816.

Keywords

Wrap restraint stress; irritable bowel syndrome; nerve structures; rat colon.