Involvement of catechol-O-methyltransferase activity in the modulation of enteric neuromotor function: implication in functional gastrointestinal disorders

1)Caputi V. 2)Marsilio I. 3)Cerantola S. 4)Contarini G. 5)Mereu M. 6)Galuppini F. 7)Rugge M. 8)Orso G. 9)Crema F. 10)Giaroni C. 11)Papaleo F. 12)Giron MC.

University of Padova Dept. of Pharmaceutical and Pharmacological Sciences

Background. Irritable bowel syndrome (IBS) is a still poorly understood functional disorder and abnormalities in gut immune/inflammatory responses and brain-gut communications have been proposed as potential determinant factors (Jones et al., 2017; Edebol-Carlman et al., 2017). Visceral hypersensitivity is evidenced in most patients with IBS probably due to both peripheral and central nervous system mechanisms (Karling et al., 2011; Fadgyas-Stanculete et al., 2014). Since both psychiatric disorders and pain syndromes are associated to low catechol-O-methyltransferase (COMT) activity and both are linked to IBS-like symptoms, we assessed whether COMT genetic reduction affects functional and structural integrity of enteric nervous system (ENS) in mice. Methods. Female COMT heterozygous (COMT+/−) and wild-type (COMT+/+, WT) mice (12±2 weeks) were used and their genotypes were confirmed by PCR on mouse tail DNAs. To evaluate ileum integrity, histological analysis was performed on ileal specimens (5-10 cm from ileocecal valve) obtained from COMT+/- and WT mice. Full-thickness distal ileum segments were mounted longitudinally in organ baths and contractility was evaluated as changes in muscle tension recorded isometrically following electric field stimulation in non-adrenergic non-cholinergic (NANC) conditions (EFS=10 Hz, 1 μM guanethidine and 1 μM atropine) with or without 0.1 mM Nω-nitro-L-arginine methyl ester (L-NAME; pan-nitric oxide synthase (NOS) inhibitor) or 0.01 mM 1400W (inhibitor of inducible NOS, iNOS). In ileal frozen sections from COMT+/− and WT mice the distribution of glial marker S100β and iNOS immunoreactivity were determined by confocal microscopy. mRNA levels of iNOS, GluN1 subunit of NMDA receptor, dopamine receptor D1 (DA1), and S100β were also studied in LMMP preparations obtained from transgenic animals. Results. Hematoxylin-eosin staining of ileal frozen sections showed a significant increase of muscle layer thickness (+87±6%, N=5, $p<0.05$) in COMT+/- mice. Significant changes in nitrergic inhibitory response after EFS at 10 Hz, performed in NANC conditions, were found in COMT+/− mice and were partially abolished by pre-treatment with the iNOS inhibitor 1400W. In the ENS of COMT+/− mice ileal distribution of iNOS and S100β immunoreactivity was significantly augmented in myenteric ganglia. The expression of the iNOS, GluN1, DA1 and S100β genes resulted significantly increased in LMMPs obtained from COMT+/− mice compared to WT (fold changes: +5.18±0.52; +1.7±0.12; +2.67±0.49; +2.56±0.37, N= 6, $p<0.05$, respectively). Conclusion. Our study provides evidence that genetic-driven COMT defective activity determines increased iNOS-dependent NO production associated to altered ENS architecture, neurochemical coding and visceral sensitivity, underlining that disturbances in the brain-gut axis are implicated in IBS pathogenesis.

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