N/OFQ AND NOP RECEPTOR SYSTEM: ROLE IN THE CONTROL OF SOME GASTROINTESTINAL ACTIVITIES IN PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

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N/OFQ and NOP receptors, widely distributed at the central and peripheral level, represent an endogenous system capable of controlling several gastrointestinal (GI) functions which may represent a new target both for a further study of the cerebral mechanisms involved in regulating GI motor and secretory activities, and for the development of new drugs to be used peripherally in all conditions of altered GI functionality. By using the natural compound N/OFQ, recently synthesized NOP agonists possessing more potent and long lasting effects, and selective NOP receptor antagonists, has been shown that: 1) the brain orphaninergic system exerts in vivo an inhibitory action on gastric emptying, GI transit, colonic propulsion and gastric secretion in rats; 2) the central inhibitory action of N/OFQ on gastric emptying in rat is controlled by the hypothalamus-adrenal axis as well as by mechanisms involving the CRF and neuronal circuits in response to stress; 3) the peripheral and central administration of N/OFQ and NOP receptor agonists significantly reduce ethanol-induced gastric damage in rat by vagal cholinergic and sympathetic pathways at CNS level, by non muscarinic vagal pathways at the peripheral level; 4) N/OFQ reduces amylase secretion only from guinea pig pancreatic lobules using cholinergic pathways and is inactive on isolated dispersed acini, indicating that NOP receptors, not present on the acinar cell, are probably located on presynaptic pancreatic neurons where they play a role in the indirect control of exocrine pancreatic secretion. Of all these effects that N/OFQ has shown to elicit at the GI tract level, a particular significance derives from the valence each of them has in certain pathological conditions of the GI apparatus due to the colon antipropulsive action, the antiulcer effect and the inhibition of the exocrine pancreatic secretion. An increase in colonic transit and faecal excretion, as well as an increased incidence of gastric lesions, actually represent the main GI alterations due to stress situations. Furthermore, colonic hypermotility is one of the main components of several intestinal inflammatory diseases. Lastly, the increased amylase content with the consequent intracellular activation of the zymogens may be a factor that favours the onset of acute pancreatitis. Therefore, the inhibitory effect of N/OFQ on colon motility, on gastric ulcers and on exocrine pancreatic secretion, assume a protective significance in the above-reported GI dysfunctions and will be exhaustively discussed.