Functional intestinal dysmotility associated with metabolic and neurological disorders: is enteric inflammation the common root?

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Functional gastrointestinal disorders (FGIDs), the most common diagnoses in gastroenterology, are characterized by digestive symptoms in the absence of overt organic abnormalities, which often occur in combination with gut dysbiosis, altered mucosal and immune functions, motility disturbances, visceral hypersensitivity, and altered central nervous system processing (Drossmann and Hasler, 2016). Molecular and cellular studies suggest that the presence of inflammation seems to hold a critical role in the onset and development of such 'functional' disorders, eliciting morphological and physiological alterations in the neuromuscular compartment and enteric sensory nerves (Drossmann and Hasler, 2016).

An increasing body of evidence points out the presence of FGIDs as comorbidities in several pathological conditions characterized by heterogeneous pathogenic hallmarks. In this regard, epidemiologic data have shown that some neurodegenerative diseases [e.g. Parkinson's disease (PD) Alzheimer's disease (AD) and multiple sclerosis] (Winge et al., 2003; Coggrave et al., 2014) and metabolic disorders (e.g. obesity, diabetes mellitus) (Fysekidis et al., 2012; Yarandi and Srinivasan, 2014) are closely associated with the occurrence of chronic abdominal complaints, most of which overlap with common functional digestive disorders, such as gastroesophageal reflux, dyspepsia, constipation, irritable bowel syndrome, diarrhea, bloating, and other non-specific conditions.

In recent years, our research team has employed some rodent models reminiscent of human neurological diseases, such as the SAMP8 mouse (a strain that develops spontaneously early learning and memory deficits, similar to those observed in AD) and nigrostriatal dopaminergic degeneration induced by 6-hydroxy dopamine in rats (PD model), or high fat diet-induced obesity in mice, with the purpose of characterizing the molecular and cellular mechanisms underlying the enteric motor abnormalities associated with neurological and metabolic disorders.

Interestingly, colonic specimens from obese mice or animal models of AD or PD displayed common features, comprising a significant increase in inflammatory cytokines (TNF and IL-1β) and oxidative stress index (malondialdehyde). Functionally, a marked impairment of electrically induced contractions was observed in colonic preparations isolated from pathologic rodents and maintained under standard conditions. Subsequent sets of experiments, aimed at pharmacologically ablating the main components of the enteric nervous system, allowed to record a marked decrease in cholinergic responses in obese mice as well as in animals with AD or PD. Of note, the animals with neurological or metabolic diseases shared also a significant enhancement of electrically-evoked tachykininergic contractions.

Our experimental findings, taken together with literature data, suggest that pathological conditions characterized by different etiopathogenic mechanisms, such as central

neurodegenerative diseases and obesity, share morpho-functional bowel alterations likely ascribable to the presence of a common condition of enteric inflammation.

References

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