Inhibitory and excitatory enteric neurons of the mouse duodenum co-express the Glucagon-like Peptide 1 or Glucagon-like Peptide 2 receptors

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Glucagon-like Peptide 1 (GLP-1) and Glucagon-like Peptide 2 (GLP-2) are two pro-glucagon-derived hormones produced by enteroendocrine L cells. These cells produce GLP-1 and GLP-2 in response to nutrient assumption and absorption, and both hormones play a critical role in the regulation of gastrointestinal motility. Their actions are mediated by specific receptors, the GLP-1R and the GLP-2R. Cellular localization of these receptors has been amply reported for the enteroendocrine cells of the intestinal epithelium while little information is available on their expression in enteric neurons. Therefore, we presently investigated, by immunohistochemistry, the presence and the distribution of these receptors in the neurons of the mouse duodenum. Furthermore, we assessed the chemical coding of the neurons expressing GLP-1R and GLP-2R by evaluating the co-localization of these receptors with inhibitory (neuronal nitric oxide synthase, nNOS) and excitatory (choline acetyltransferase, ChAT) neurotransmitters. GLP-1R-immunoreactivity (IR) and GLP-2R-IR were detected in some myenteric neurons and GLP-2R-IR also in some submucosal neurons. GLP-1R-IR nerve fibers were not seen outside the ganglia, while GLP-2R-IR nerve fibers were present in the circular muscle layer and at the deep muscular plexus. No other cell type showed either GLP-1R- or GLP-2R-IR. The mean number of GLP-1R-IR myenteric neurons/slice was 14.3 ± 1.4; the mean number of GLP-2R-IR myenteric neurons/slice was 27.7 ± 0.9 and that of the submucosal neurons was 1.4 ± 0.3 neurons/slice. GLP-1R/nNOS double labelling showed that 27.22 ± 3.14% of the GLP-1R myenteric neurons co-expressed nNOS-IR; instead the GLP-1R neurons that co-expressed ChAT-IR were very few, <1/slice. GLP-2R/nNOS double labelling showed that 8.74 ± 1% of the GLP-2R-IR myenteric neurons co-expressed nNOS-IR and GLP-2R-IR/ChAT double labelling demonstrated that 69.93 ± 8.43% of the GLP-2R-IR myenteric neurons co-expressed ChAT-IR. These data confirm that both GLP-1 and GLP-2 play an important role in the regulation of gastrointestinal motility. In particular, although both GLP-1 and GLP-2 are able to indirectly inhibit the motility by modulation of NO release, GLP-1 seems to play a main role. On the other hand, the GLP-2 is also able to directly inhibit gastrointestinal motility by inhibiting the acetylcholine release and this pathway seems to be the most consistent. Finally, the present results indicate that the GLP-2R might mediate an inhibitory or excitatory action depending on the neuronal cell type in which it is expressed.