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NEUROGASTROENTEROLOGY

Colonic motor neurotransmission—is β-NAD$^+$ in control?

Normal gastrointestinal motility relies upon effective neural control, which is provided by inhibitory and excitatory motor neurons. Inhibitory neural regulation is mediated by the release of at least two neurotransmitters—nitric oxide and a purine—from intrinsic inhibitory motor neurons with cell bodies in the myenteric plexus; the purine responsible for mediating these inhibitory responses has, however, remained controversial. Findings published in *Neurogastroenterology & Motility* now indicate that β-nicotinamide adenine dinucleotide (β-NAD$^+$) serves as the purinergic inhibitory neurotransmitter.

Findings from previous reports had suggested that both ATP and β-NAD$^+$ act as purinergic inhibitory neurotransmitters in the colon. "The methodological approach used in many of these studies, however, did not enable the sites of purine release to be effectively distinguished," explains one of the authors from the study, Kenton Sanders. Here, the researchers used high-performance liquid chromatography to specifically analyse which purines were released after stimulation of the receptors expressed on motor neurons in the myenteric plexus of both mice and primates.

Ganglionic stimulation yielded release of the purines ATP and β-NAD$^+$ from the *tunica muscularis* of the monkey and mouse colon; release of these purines was dependent upon the presence of myenteric ganglia.

"Interestingly, the application of toxins that block action potentials or Ca^{2+} entry at motor nerve endings inhibited the release of β-NAD$^+$, but had no effect on ATP release," states Sanders. The release of β-NAD$^+$ therefore seems to require nerve action potentials and junctional mechanisms that are known to be essential for neurotransmission. By contrast, these findings suggest that ATP is released from nerve cell bodies within the myenteric ganglia, but not from the nerve terminals of motor neurons.

The authors of this study concluded that β-NAD$^+$ or one of its metabolites—and not ATP—is the purinergic inhibitory neurotransmitter in the colon. Further research is now required to better understand this inhibitory pathway, which has the potential to be harnessed for the therapeutic regulation of colonic motility and so provide relief for individuals with gastrointestinal motility disorders and enteric pain.

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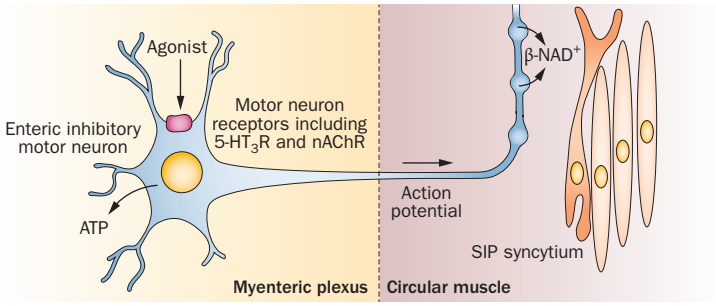
Original article Durnin, L. *et al.* Differential release of β-NAD$^+$ and ATP upon activation of enteric motor neurons in primate and murine colons. *Neurogastroenterol. Motil.* doi:10.1111/nmo.12069



Ganglionic stimulation of motor neurons causes release of β-NAD$^+$ at nerve varicosities. Abbreviations: β-NAD$^+$, β-nicotinamide adenine dinucleotide; 5-HT$_3$R, serotonergic receptors; nAChR, nicotinic acetylcholine receptors; SIP, smooth muscle cells, interstitial cells of Cajal, platelet-derived growth factor receptor positive cells.