CORRESPONDENCE

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Evidence for β-Nicotinamide Adenine Dinucleotide as a Purinergic, Inhibitory Neurotransmitter in Doubt

Dear Sir:

We read with interest a recent report by Hwang and colleagues[1] suggesting that β-nicotinamide adenine dinucleotide (β-NAD) as opposed to adenosine triphosphate (ATP) is the purinergic neurotransmitter mediating purinergic fast inhibitory junction potential (fIJP) and relaxation in human and primate colon, following a similar conclusion in mouse colon.[1–3] We believe that the authors' conclusions are not supported by their own data or information available in the literature.

The authors advance 2 reasons to support their conclusion: (1) Pharmacology of the action of ATP does not mimic that of the purinergic fast IJP; (2) ATP from the muscle strips is not released from the purinergic vesicles. However, these assertions do not stand careful scrutiny.

The authors report that exogenous ATP causes transient hyperpolarization that is not blocked by selective P2Y1 receptor antagonists in concentrations that block the purinergic fIJP.[1,2] This group has also reported that the P2Y1 receptors mediating the purinergic IJP are present on fibroblast-like cells ([FLC]; also named PDGFRα cells[4]). Electrical hyperpolarization in the fibroblast-like cells is thought to be transmitted to the smooth muscle cells. Based on the insensitivity of ATP on P2Y1 receptors in muscle strips, it was expected that ATP would not activate P2Y1 receptors on fibroblast-like cells.[1] However, the authors[4] found that ATP effectively stimulated these P2Y1 receptors on the fibroblast-like cells. These observations are not consistent with the reported lack of effect of ATP on P2Y1 receptors in muscle strips.[1,2]

Published reports from several different laboratories also fail to support the view that the pharmacology of ATP- or ADP-induced hyperpolarization is different from that of the purinergic fIJP. Numerous studies in a variety of gut tissues, including human colon, report that ATP potently causes smooth muscle hyperpolarization and inhibition of spontaneous contractions via P2Y1 receptor stimulation.[5,6]

It is also worth noting that as compared to ATP, β-NAD is a very weak agonist of the P2Y1 on fibrobast-like cells [4], human colon muscle strips.[1–2,6] In P2Y1-expressing HEK cells, β-NAD is almost 1000-fold less potent than ATP or ADP β S.[2,6]

Hwang et al[1] also reported data suggesting that ATP was not released from nerve terminals. However, ATP is known to be rapidly metabolized after release by the ectonucleotidases. Measurements of ATP and other purines made in muscle strips over longer time periods after the IJP is over may not provide information regarding the mediator of the purinergic fIJP because ATP and other candidate purines have multiple cellular origins as well as varying rates of extracellular metabolism. In contrast to the muscle strips, studies in isolated enteric varicosities have shown that ATP was released upon their depolarization.[7] Hwang and colleagues[1] also report that in their studies, quantitatively more β-NAD was released than ATP. However, because of the very rapid degradation of ATP, these results are difficult to interpret.

In summary, the available data support the view that ATP/ADP, as opposed to β-NAD, is the most likely candidate responsible for the P2Y1 receptor-mediated purinergic IJP in the gut.

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Reply. Purinergic neurotransmission has long been controversial with respect to the identity of the transmitter substances and post-junctional targets that mediate inhibition. We have shown that several criteria for a substance to be considered a neurotransmitter are better satisfied by another purine, β-NAD, than by ATP in human, monkey, and mouse colons.[1,2] Thus, β-NAD likely contributes to purinergic neurotransmission in the gut.

Unfortunately, Dr Goyal appears to have misread or misinterpreted some statements made in our recent paper.[1] For example, we never stated that ATP is not released from purinergic vesicles; in fact we did not use the term purinergic vesicles. We showed that the release of ATP (and metabolite ADP) does not follow release character-