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Title: CCK-elicited pancreatic Ca^{2+} signal generation is probably not initiated by IP_3 formation

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Letter 2 to Editor

CCK-elicited pancreatic Ca^{2+} signal generation is probably not initiated by IP_3 formation

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David Yule's (Yule, 2025) - responding to my letter (Petersen, 2025) about Takano et al.'s (2025) original paper in the Journal of Physiology - concludes that "*Physiologically, the neurotransmitter ACh and gut hormone CCK both result in IP_3 (and cADPr) generation, whereas CCK stimulation additionally results in NAADP formation. The latter contributes to the specific differences in the spatiotemporal characteristics of Ca^{2+} signals observed by each secretagogue.*" According to this hypothesis, one would logically predict that specific inactivation of NAADP receptors should not block or inhibit CCK-elicited Ca^{2+} signal generation but change the typical CCK Ca^{2+} signal pattern to the one typical for ACh (Carl Petersen et al., 1991, Yule et al., 1991). However, this is not what has been observed experimentally. Two different ways of blocking the intracellular NAADP receptors, that both have no effect on Ca^{2+} signals generated by ACh, have been shown repeatedly to abolish Ca^{2+} signal generation elicited by physiologically relevant CCK concentrations (Cancela et al., 2000; Petersen et al., 2021; Petersen, 2025). Yule's hypothesis (2025) does not explain why IP_3 generated by ACh stimulation initiates Ca^{2+} signalling, whereas IP_3 postulated to be produced by CCK stimulation is unable to do so.

I agree with David Yule that there are technical limitations concerning measurements of small changes in IP_3 levels (Petersen, 2025) and I also agree that it is difficult to assess the ACh concentration near the muscarinic receptor sites during physiological nerve stimulation (Yule, 2025). However, irrespective of the desire for more sensitive IP_3 measurements and more clarity about physiological stimulation levels, it is already clear that ACh, at all concentrations eliciting Ca^{2+} signals, must act via IP_3 generation, because there is no alternative explanation. It is equally clear that even if a physiological CCK concentration does in fact elicit a small rise in the intracellular IP_3 level, it is insufficient for Ca^{2+} signal generation. David Yule's hypothesis is therefore not supported by the currently available data.

The model presented by Petersen et al. (2021 – Fig. 2), based on the original concept proposed by Cancela et al. (2000), differentiates between two separate initiating signal transduction pathways (for ACh via IP_3 and for CCK via NAADP [and possibly cyclic ADP-ribose]) and a final common Ca^{2+} signal oscillator (combination of IP_3 and Ryanodine receptors). This model is, as far as I can see, compatible with all currently available data.

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