Reply to “Letter to the editor: Parasympathetic innervation of the rodent spleen?”

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REPLY: The parasympathetic innervation of the spleen is a matter of debate since Dale’s isolation of ACh from the spleen (6). The letter by Anderson and colleagues (1) represents a fair contribution to this discussion. Based on their constructive comments, we suggest further studies on the functional and integrative nature of this parasympathetic spleen innervation, allowing to decipher the physiology of the parasympathetic nerves for the spleen.

Previously, by the lesioning of nerve branches entering the spleen one by one, specific nerves were identified that connect with the dorsal motor nuclei of the vagus (DMV). Upon the lesioning of the nerves at both tips of the spleen, which were often covered by connective tissue blocks, injections with the pseudorabies virus (4) or cholera toxin subunit B (5) neuronal tracers failed to label the DMV, while labelling of the sympathetic motor neurons in the intermediolateral nucleus was unaffected. The surgical procedure has been described in detail by Buijs et al. (4), and the controls in this first study consisted of pseudorabies virus injections in the spleen of mice that prior received sympathetic and parasympathetic denervation of the spleen. These controls revealed no sign of infection in the brain or spinal cord, thereby excluding inadvertent spread of the tracer to vagal fibres located nearby. In addition, the fact that labelled neurons in the DMV were demonstrated after sympathetic denervation illustrates that DMV labeling does not arise from labeling via the sympathetic celiac-superior mesenteric plexus ganglion.

Unfortunately, we were not able to identify the specific neurotransmitters involved or structures targeted by the vagal nerve terminals in the spleen. The nerves identified as being parasympathetic were, as expected, negative for tyrosine hydroxylase, and like Anderson and colleagues (1), we did not detect expression of choline acetyl transferase within the spleen. However, the absence of acetylcholine is not sufficient proof for the absence of direct input from the vagus. For example, we (2, 3) and others (9) have shown the presence and function of vagal innervation of the liver while also in the liver choline acetyltransferase or vesicular acetylcholine transporter staining is absent.

For the spleen, it has been suggested that both the parasympathetic and sympathetic system act together to restrain inflammation (8, 10). Consistent with this notion, we observed striking similarities in the effects on the immune system upon sympathetic- and parasympathetic denervation of the spleen (7). Interestingly, LPS-induced antibody production appeared to be fully dependent on the parasympathetic nerve branches, and LPS increased activation of brain sites that connect to the spleen through the parasympathetic nerve branches (4). It is important to note that these observations were only done in the mouse, and no other species was investigated.

Overall, neuroanatomical and functional evidence for the existence of parasympathetic innervation of the spleen in mouse exists (4, 5, 7), although species differences, as indicated by the letter of Anderson and colleagues (8), may exist as well. Agreeably, future research needs to establish the neural coding and functional relevance of such parasympathetic innervation, as well as studying its integration with the more commonly known sympathetic innervation of the spleen.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

S.K. drafted manuscript; S.K., W.J.D.J., and P.C.N.R. edited, revised, and approved final version of manuscript.

REFERENCES


