Letter to the editor: Parasympathetic innervation of the rodent spleen?

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TO THE EDITOR: In a recent issue of the American Journal of Physiology-Heart and Circulatory Physiology, we were interested to read the article, “Splenic autonomic denervation increases inflammatory status, but does not aggravate atherosclerotic lesion development,” in which Kooijman and coauthors (8) described the proinflammatory consequences of selectively cutting the sympathetic and parasympathetic nerve supplies to the spleen in mice.

Many workers in the field doubt that the rodent spleen receives parasympathetic innervation (1, 5, 7, 9), but some (2, 3), though not all (4), previous articles from this group argue that it does. The evidence in favor is based on finding labeled neurons in the dorsal motor nucleus of vagus (DMV) after injection into the spleen of either the transynaptic tracer pseudorabies virus (2) or the conventional retrogradely transported tracer cholera toxin subunit B (3), which does not traverse synapses. At face value, the latter finding implies the presence of preganglionic vagal fibers (and thus, presumptively, also parasympathetic ganglion cells) within the spleen parenchyma. The alternative explanation is that labeling in DMV in these experiments was due to inadvertent spread of the tracer to vagal fibers located nearby. In this context, Fox and Powley (6) demonstrated the ease with which retrogradely transported tracers injected into abdominal organs can spread to cause artifactual labeling of DMV neurons. These workers showed that when adequate steps were taken to prevent that spread, injection of the conventional tracer True Blue into the tip of the pancreas no longer labeled DMV preganglionic neurons. Moreover, a previous viral tracing study by Cano and colleagues (5) found that pseudorabies virus injected into the rat spleen caused no labeling of DMV preganglionic neurons.

The present article by Kooijman et al. (8) and the previous study by Buijs et al. (2) identified fine nerves entering the tip of the spleen or tips of the spleen and described them as vagal parasympathetic. They showed cartoons of this innervation, but no histology. In rats and mice we have failed to find such nerves.

What we have seen on occasion are nerves following vessels distinct from the main vascular tree, entering the hilar edge of the spleen quite close to its tip. But when examined immunohistochemically, those nerves stained positively for tyrosine hydroxylase, demonstrating that they were sympathetic. We have also used the method of Gautron and coworkers (7) to enhance the detectability of cholinergic nerves by using mice that express a fluorescent label driven by the choline acetyltransferase promoter. Paying special attention to the spleen tips, we observed no cholinergic nerves entering the spleen, nor could we identify any cholinergic nerve tracts or neurons within the spleen.

In the absence of histological evidence, we therefore remain skeptical about any vagal parasympathetic innervation of the rodent spleen. Nevertheless, the “parasympathetic denervation” maneuver employed by Kooijman et al. (8) clearly had functional consequences, which we suggest could have been due to cutting sympathetic nerves. The similarity of the effects of their “sympathetic” and “parasympathetic” denervation procedures adds plausibility to this conjecture, but we remain open to alternative explanations.

DISCLOSURES

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AUTHOR CONTRIBUTIONS


REFERENCES