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Commentary

Autonomic Dysfunction: A Predictive Factor of Risk to Develop Rheumatoid Arthritis?

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In this issue of *EBioMedicine*, Koopman et al. report that autonomic dysfunction precedes the development of rheumatoid arthritis (RA) (Koopman et al., 2016). They observe lower parasympathetic activity, and a decreased expression level of the parasympathetic α7nicotinic acetylcholine receptor (α7nAChR) on peripheral blood monocytes, and higher sympathetic hormone (norepinephrine) in patients at risk to develop RA. Their interpretation is that autonomic dysfunction would play a role in the etiopathogenesis of RA rather than being the result of chronic inflammation.

The autonomic nervous system (ANS) is the bidirectional link between the central nervous system and the rest of the organism. The ANS is composed of the sympathetic and the parasympathetic nervous system, i.e. the vagus nerves (VN), the largest visceral sensory nerves in the body, and the sacral parasympathetic nucleus. These are mixed nerves containing 80–90% of afferent fibres for the VN and 50% of afferent fibres for the sympathetic nervous system. Vagal afferents end in the nucleus tractus solitarius, in the medulla, while sympathetic afferents end in the spinal cord. From there, projections reach the central autonomic nervous system (CAN) which integrates and modulates afferent information from the organism in brain regions involved in the autonomic, endocrine, motor, and behavioral responses such as the hypothalamus, the limbic system, and the prefrontal cortex (Benarroch, 1993). In return, the CAN generates autonomic responses via projections to preganglionic sympathetic neurons in the spinal cord and parasympathetic neurons of the dorsal motor nucleus of the VN in the medulla to modulate the ANS and thus the vagal tone. The CAN is sensitive to interoceptive (from the inner medium) or exteroceptive (environmental) information and chronic activation of the CAN is able to generate dysautonomia.

There is normally a balance between the parasympathetic and sympathetic nervous systems. An imbalance of the ANS has been described in RA, inflammatory bowel disease (IBD) (Pellissier et al., 2010), and others. Generally, this imbalance is interpreted as a consequence of the disease more than a cause. However, Thayer JF (Thayer and Lane, 2007) has shown that decreased vagal function precedes the development of a number of risk factors for cardiovascular disease and that modification of risk profiles in the direction of lower risk is associated with increased vagal function. Vagal tone is explored via the cardiac vagal tone by means of heart rate variability (HRV) measurement (Task Force, 1996). HRV is a marker of the sympatho-vagal balance where the LF/HF ratio is calculated as a global marker of the autonomic balance where LF (low frequency) represents the sympathetic tone and HF (high frequency) the parasympathetic (i.e. vagal) tone. The cardiac vagal tone and HRV have allowed the construction of the neurovisceral integration model that includes the CAN. A decreased HRV at rest reflects a low vagal tone and could be considered as a marker of stress. A high level of HRV is associated with good health and well-being and good resilience in emotional self-regulation. HRV may be a novel, useful predictor of response to anti-TNF therapy in patients with inflammatory arthritis and others, and emphasizes the importance of autonomic influence of autoimmune disease expression. The prefrontal cortex regulates peripheral immune cells through the autonomic and neuroendocrine pathways and controls vagal tone by modulating the VN efferent outflow. Increased inflammatory markers, e.g. C reactive protein and interleukin-6, are associated with decreased HRV. We have described an imbalance between the hypothalamic pituitary adrenal (HPA) axis and vagal tone in Crohn's disease patients and highlighted the specific homeostatic link between a low vagal tone and TNFα in these patients (Pellissier et al., 2014).

The VN has a dual anti-inflammatory effect both through its afferent fibers activating the HPA axis and, more recently, through its efferent fibres, i.e. the cholinergic anti-inflammatory pathway (CAP) where ACh inhibits the release of TNFα by macrophages after binding to α7nAChR (Pavlov and Tracey, 2015). A vago-sympathetic pathway where the VN stimulates the splenic nerve thus inhibiting the release of TNFα by spleen macrophages has been evoked (Pavlov and Tracey, 2015) but debated by others. There is very few data, except in the cardiovascular domain, regarding the fact that autonomic dysfunction precedes inflammatory diseases. Low vagal tone is a significant predictor of necrotizing enterocolitis in pre-term infants (Doheny et al., 2014). The present results of Koopman et al. are very important since one can imagine that restoring a normal vagal tone by targeting the CAP could either prevent the development of inflammatory disorders such as RA, IBD and others and/or prevent a flare of the disease in such patients with an imbalance of the ANS. Among such targets could be drugs such as

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α7nAChR agonists, drugs activating the central cholinergic pathway, such as galantamine, or non-drug therapies such as physical exercise, complementary therapy such as hypnosis, cognitive behavioral therapies, known to improve vagal tone. VN stimulation (VNS) either invasive or non-invasive could be of interest. We have recently shown, in a pilot study performed in patients with mild to moderate CD, that invasive VNS improves these patients and restores vagal tone but further investigation is warranted (Bonaz et al., 2016). VNS studies are also ongoing in RA (Koopman et al., 2012). Ideally, a chronic recording of vagal tone in patients susceptible to develop inflammatory disorders would be of interest. In the same way, a technique which could restore vagal tone based on this recording would be of interest.

As stated by the authors, identification of additional risk factors for RA is necessary to provide insight into pathogenic mechanisms contributing to the development of clinically manifest disease, and might also lead to development of novel preventive strategies. The characterization of the sympathovagal balance would be of interest in RA, but also other inflammatory disorders, such as IBD. This parameter should be part of the evaluation of these patients in addition to clinical, biological (inflammatory), and morphological parameters.

Disclosure

The author declared no conflicts of interest.

References

Benarroch, E.E., 1993. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin. Proc. 68, 988–1001.

Bonaz, B., et al., 2016. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. Neurogastroenterol. Motil. (Feb 27).

Doheny, K.K., et al., 2014. Diminished vagal tone is a predictive biomarker of necrotizing enterocolitis-risk in preterm infants. Neurogastroenterol. Motil. 26, 832–840.

Koopman, F.A., et al., 2012. Pilot study of stimulation of the cholinergic anti-inflammatory pathway with an implantable vagus nerve stimulation device in patients with rheumatoid arthritis. Arthritis Rheum. 64 (Suppl) (Abs 451).

Koopman, F.A., et al., 2016. Autonomic dysfunction precedes development of rheumatoid arthritis: a prospective cohort study. EBioMedicine 6, 231–237.

Pavlov, V.A., Tracey, K.J., 2015. Neural circuitry and immunity. Immunol. Res. 63, 38–57.

Pellissier, S., et al., 2010. Psychological adjustment and autonomic disturbances in inflammatory bowel diseases and irritable bowel syndrome. Psychoneuroendocrinology 35, 653–662.

Pellissier, S., et al., 2014. Relationship between vagal tone, cortisol, TNF-alpha, epinephrine and negative effects in Crohn's disease and irritable bowel syndrome. PLoS One 9, e105328.

Task Force of the European Society of Cardiology and the North American Society of Pacingand Electrophysiology, 1996r. Heart rate variability. standards of measurement, physiological interpretation, and clinical use. Eur. Heart J. 17, 354–381 ([No authors listed]).

Thayer, J.F., Lane, R.D., 2007. The role of vagal function in the risk for cardiovascular disease and mortality. Biol. Psychol. 74, 224–242.