PERSPECTIVES

Cardiac defibrillator neurones

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The cardiac vagal motor system exerts a myriad of actions upon the beating mammalian heart and its nutrient vascular supply, but one of its most fascinating actions is to quell potentially lethal arrhythmias. It has been recognised for a long time that the amount of nervous vagal tone to a heart has a direct bearing on the outcome of potentially fatal cardiac arrhythmias following a heart attack (La Rovere *et al.* 1998). Life and death in a coronary care unit is sometimes governed by cardiac vagal tone. In 2007, Brack *et al.* provided evidence that nitric oxide mediates the protective effect of the vagi on ventricular fibrillation. In this issue of *The Journal of Physiology* this group has succeeded in measuring nitric oxide release in the beating left ventricle in response to vagal stimulation (Brack *et al.* 2009). One interpretation of this work is that there is a population of cardiac nitrergic postganglionic neurones which project to the left ventricle and protect it from fibrillation. This is the conception that I am drawn to, being richer in possibilities than other hypotheses.

For almost 10 years this group of physiologists and cardiologists has employed the century old method of Oscar Langendorff but with a twist; they leave the cardiac autonomic nerves attached. Like countless investigators before them, they have shown that there is no vagal inotropic effect on the left ventricle, provided the heart rate is maintained constant. Interestingly they have reported that the vagus can affect dispersion of ventricular repolarisation (Mantravadi *et al.* 2007). This was followed by experiments that showed vagal stimulation could also raise the ventricular threshold to fibrillation. Pharmacological experimentation provided evidence that nitric oxide (NO) mediates this vagal protection via effects on action potential duration restitution (Brack *et al.* 2007). The next logical step is described in this issue of *The Journal of Physiology*: to detect an increase of NO in the wall of the left ventricle during vagal stimulation (Brack *et al.* 2009). The question arises: what is the source of this NO? Is it nitrergic nerves or nitrergic myocytes? The burst of NO is probably not due to constriction and ischaemia causing increased NO production due to disturbed energy metabolism (because vagus nerve stimulation did not increase perfusion pressure under constant flow conditions i.e. did not increase coronary resistance). One caveat is that the researchers measured pressure a little remotely from the ostia of the coronary arteries. Of note, the NO increase also occurred in response to acetylcholine infusion, but this was not blocked by an antagonist of the neuronal form of NO synthase. In contrast, the vagally released NO was sensitive to this antagonist. If the NO is from nitrergic nerves then the heart should contain these NO-producing postganglionic neurones. There is no difficulty in finding supportive evidence for this proposal in many species e.g. 37% of human cardiac ganglion neurones contain NO synthase (Singh *et al.* 2009). The work of Brack *et al.* (2009) should act as a stimulus to trace the trajectory of these NOS-positive neurones within atrial ganglionated plexuses. The question of vagal innervation of mammalian ventricles may have become embroiled in controversy in the past, partly because there has been too much emphasis on cholinergic markers. The paper is a testament to the ingenuity of its authors and an enduring method of Carl Ludwig who in 1866, together with Elias Cyon created the first isolated perfused frog heart.

References

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