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Blood pressure regulation by C1 neurons in the rostral ventrolateral medulla: new light on the subject

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Thirty-five years ago two papers were published that were to have a profound impact on our understanding of the central mechanisms regulating blood pressure. In one of these papers, Guertzenstein & Silver (1974) reported that bilateral application of the inhibitory amino acid glycine to a discrete region on the ventrolateral surface of the rostral part of the medulla oblongata in anaesthetized cats resulted in a very large fall in blood pressure. Since glycine inhibits neuronal cell bodies but does not affect fibres of passage, these observations indicated that there are neurons, located close to the ventrolateral surface of the rostral medulla, that provide a tonic excitatory drive to the spinal sympathetic outflow which maintains a normal level of resting blood pressure.

In another study published in the same year, Hökfelt *et al.* (1974) used the newly developed method of immunohistochemistry to demonstrate the existence of neurons within the rat brain that contain the enzyme phenylethanolamine-*N*-methyltransferase (PNMT), a marker of adrenaline-synthesising neurons. Such neurons were essentially confined to two discrete groups, one of which was in the rostral part of the ventrolateral medulla (RVLM), which Hökfelt *et al.* (1974) designated the C1 group. Later studies demonstrated that there are homologous groups of neurons in the RVLM of other mammalian species, including humans.

Hökfelt *et al.* (1974) also noted that PNMT-containing terminals were densely located in the intermediolateral cell column of the spinal cord, and they suggested that these may arise from the C1 neurons in the RVLM. Later studies confirmed this, and further showed a striking correspondence between the location of C1 neurons in the RVLM and sites at which chemical or electrical stimulation increases blood pressure and sympathetic vasomotor activity (Dampney *et al.* 1985; Reis *et al.* 1988). Furthermore, bilateral destruction or inhibition of the RVLM region greatly attenuated the baroreceptor and other cardiovascular reflexes (Dampney *et al.* 1985; Reis *et al.* 1988). These early observations led to the view that the C1 neurons are sympathoexcitatory and have a critical role in the tonic and reflex control of sympathetic vasomotor activity.

However, in a paper published in this issue of *The Journal of Physiology*, Abbott *et al.* (2009*b*) point out that other observations have cast some doubt on this commonly held view of the function of C1 neurons in sympathetic regulation. In particular, a significant proportion (about one-third) of neurons in the RVLM that project directly to the spinal sympathetic outflow are not C1 cells. Conceivably, these non-C1 cells, rather than C1 cells, could be largely responsible for the regulation of sympathetic vasomotor activity by RVLM neurons. Indeed, after destruction of the large majority (>80%) of C1 neurons by the use of a selective toxin that leaves non-C1 neurons in the RVLM intact, resting sympathetic activity is not significantly reduced in anaesthetized rats (for references see Abbott *et al.* 2009*b*).

In their study, Abbott *et al.* (2009*b*) used an optogenetic method in which channelrhodopsin-2 (ChR2), a light-sensitive channel, was selectively expressed in catecholamine-containing neurons in the RVLM (i.e. C1 neurons) using a lentivirus under the control of a catecholamine neuron-preferring promoter. The vast majority (89%) of neurons that expressed ChR2 also contained Phox2b, a transcription factor that is found almost exclusively within C1 cells as well as chemosensitive neurons in the retrotrapezoid nucleus located just rostral to the RVLM region (Abbott *et al.* 2009*a*). Photostimulation using laser light pulses directed specifically at the C1 region resulted in increases in blood pressure and splanchnic sympathetic nerve activity. These effects could not be attributed to activation of the chemosensitive neurons in the retrotrapezoid nucleus, because stimulation of these neurons does not evoke a cardiovascular response (Abbott *et al.* 2009*a*). Furthermore, the authors were able to confirm by using single unit recordings in combination with the juxtacellular labelling method that RVLM neurons whose activity was strongly entrained to the light pulses all contained ChR2, while those whose activity was unrelated to the stimulus did not contain ChR2. These observations indicate that the method is an effective way of selectively activating a defined subset of neurons, and also provide strong evidence that selective activation of C1 neurons increases sympathetic vasomotor activity and blood pressure, confirming the traditional view of the role of these neurons (Dampney *et al.* 1985; Reis *et al.* 1988).

One very interesting feature of the results reported by Abbott *et al.* (2009*b*) is that individual RVLM neurons (presumably C1 neurons) that were activated by light pulses applied at a frequency of 20 Hz typically responded with a single action potential for each pulse, in a highly repeatable fashion. There was no reduction in the responsiveness of single RVLM neurons with high frequency stimulation, whereas recordings of splanchnic sympathetic activity showed that each single light pulse evoked a large initial peak of sympathoactivation followed by a period of sympathoinhibition that lasted for over one second. The authors suggest that this post-excitation inhibition is a property of the sympathetic preganglionic neurons, which may be modulated by inputs to these neurons from other sources, such as the raphe nuclei or the hypothalamus. The ability to activate C1 neurons in a highly selective and reproducible way should allow this hypothesis to be tested in future studies. It could also be used to examine other unanswered questions, such as whether C1 neurons in the RVLM activate all or only specific subsets of sympathetic neurons regulating different vascular beds.

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