Medullary pathways regulating sympathetic outflow: the need for more lateral thinking

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STUDIES CARRIED OUT more than 50 years ago demonstrated that electrical stimulation of sites within a large part of the dorso-lateral reticular formation in the medulla oblongata can produce large increases in arterial pressure (1, 21). These early studies led to the view that neurons controlling the sympathetic outflow to the heart and blood vessels are distributed diffusely throughout this pontomedullary area. In the 1980s, however, attention shifted to the role of the ventrolateral medulla in cardiovascular regulation, when a series of functional and anatomical studies carried out by several laboratories led to the discovery that a discrete group of spinally projecting neurons within the rostral ventrolateral medulla (RVLM) is of crucial importance in the tonic and phasic control of sympathetic vasomotor activity and arterial pressure (for reviews, see Refs. 6, 8, 11). Around the same time, it was also discovered that there are neurons within the caudal ventrolateral medulla (CVLM) that, when excited, produce depressor and sympathoinhibitory effects (5, 6). Furthermore, experiments in the rat and rabbit demonstrated that some CVLM neurons are a critical component in the central baroreceptor reflex pathway by relaying baroreceptor inhibitory inputs to RVLM sympathethic premotor neurons (6, 8, 11).

The fact that profound pressor effects can be produced by electrical stimulation of sites within a large part of the dorso-lateral medulla is believed to reflect the fact that, at least to a large extent, these responses arise from excitation of axons of passage rather than neuronal cell bodies. Nevertheless, electrophysiological studies carried out by Drs. Barman and Gebber and their coworkers during the 1980s demonstrated that there are neurons within the dorsolateral reticular formation that have firing patterns indicative of neurons that regulate the sympathetic outflow to the heart and blood vessels. This group focused their attention on the medullary lateral tegmental field (LTF), which lies within the dorsolateral reticular formation and includes portions of the nucleus reticularis parvocellularis and nucleus reticularis ventralis (19). In these early studies, Drs. Barman and Gebber (9) demonstrated that many LTF neurons with sympathetic-related activity responded to baroreceptor inputs, either by a decrease in their firing rate or an increase. LTF neurons inhibited by baroreceptor inputs (putative sympathoexcitatory neurons) and those excited by baroreceptor inputs (putative sympathoinhibitory neurons) project to the regions containing sympathethic premotor neurons in the RVLM and midline raphe, respectively (2–4).

A more recent study from the same group demonstrated that blockade of N-methyl-d-aspartate (NMDA) receptors in the LTF abolished baroreceptor reflex control of sympathetic activity (19), indicating for the first time that LTF neurons do not merely receive inputs from baroreceptors, but are an essential link in the central pathways mediating the baroreceptor-sympathetic reflex. This was an important observation, because until that time the generally accepted model of the medullary baroreceptor reflex pathway did not include LTF neurons as a critical component (6, 8, 11). The study by Orer et al. (19) also made a further observation: blockade of non-NMDA receptors in the LTF reduced the basal level of sympathetic discharge, but without affecting baroreflex control of sympathetic discharge. Thus this group has proposed that LTF sympathoexcitatory neurons play an important role in both the tonic and baroreflex control of the sympathetic vasomotor outflow, via activation of non-NMDA and NMDA receptors, respectively.

The latest study by this group (20) in this issue of American Journal of Physiology-Regulatory, Integrative and Comparative Physiology shows that non-NMDA receptors in the LTF are also an important component of the central pathways subserving reflex sympathoexcitatory responses to some, but not all, stimuli. In particular, they found that blockade of non-NMDA receptors in the LTF significantly attenuated the reflex increase in cardiac and vertebral sympathetic nerve activity evoked by electrical stimulation of vagal afferents or by activation of arterial chemoreceptors. On the other hand, the reflex sympathoexcitation evoked by electrical stimulation of trigeminal or sciatic nerve afferents or of sites in the posterior hypothalamus or midbrain periaqueductal gray were not attenuated. As the authors point out, vagal and chemoreceptor afferent fibers (like baroreceptor afferent fibers) terminate in the nucleus of the solitary tract (NTS), whereas trigeminal and sciatic afferents do not, suggesting the possibility that, at least in the cat, the LTF may be a critical component in all sympathetic reflex pathways in which the primary afferents terminate in the NTS.

How do these observations fit in with the currently accepted functional organization of cardiovascular reflex pathways in the medulla, which are based largely on experiments in the rat and rabbit? To take the example of the chemoreceptor-sympathetic reflex, an electromyographical study in the rat by Koshiya and Guyenet (14) showed that about one-third of NTS neurons that were antidromically activated from the RVLM could be activated by chemoreceptor stimulation. Consistent with this, Hirooka et al. (12) showed that hypoxia in the conscious rabbit induced c-fos expression (indicative of neuronal activation) in a similar proportion of NTS neurons that were retrogradely labeled from the RVLM. These studies in the rat and rabbit thus support the hypothesis that chemosensitive neurons in the NTS convey excitatory inputs to RVLM sympathoexcitatory neurons via a direct pathway, rather than an indirect pathway including the LTF, as suggested by Orer and coworkers.

These observations in the rat and rabbit would be compatible with the findings reported by Orer et al. (20) in the cat if there are separate parallel pathways by which chemoreceptor signals...
are conveyed from the NTS to the RVLM, one of which includes a synapse on LTF neurons (see Fig. 1). Similarly, the medullary pathways conveying excitatory inputs from vagal afferents to the RVLM via the NTS could also consist of both direct and indirect parallel components. Such an organization is consistent with the previous observation that the chemoreceptor-sympathetic reflex is abolished by blockade of glutamate receptors in the RVLM (15).

As already mentioned, a previous study from the laboratory of Barman and Gebber and coworkers (19) demonstrated that blockade of NMDA receptors in the LTF abolishes baroreceptor reflex inhibition of sympathetic activity. Previously, however, it was shown in both the rat (7, 10) and rabbit (17) that the baroreceptor-sympathetic reflex is also abolished or greatly reduced by inhibition of neurons in a restricted region within the CVLM. This raises an important question: assuming that the functional organization of the medullary pathways subserving the baroreceptor reflex in the cat is not fundamentally different from that in the rat or rabbit, how can these different observations be reconciled? One possibility that should be considered is that the LTF neurons in the cat that relay baroreceptor signals to RVLM sympathetic premotor neurons are homologous to the baroreceptor inhibitory interneurons that have been identified within the CVLM in the rat and rabbit. This would imply that they are displaced by a considerable distance with respect to the CVLM. Nevertheless, this is conceivable, because the LTF is immediately adjacent to the rostral part of the CVLM (19). Furthermore, in both the LTF of the cat and the RVLM of the rat the baroreceptor reflex is mediated by NMDA receptors (10, 19). It is also important to note that Orer et al. (19) also showed that blockade of NMDA receptors within the rostral and/or caudal CVLM of the cat did not prevent baroreflex sympathoinhibition, although this was abolished by blockade of NMDA receptors within the LTF.

As Orer et al. (19) pointed out, the role of the CVLM in mediating the baroreceptor reflex in the cat needs to be evaluated more fully. Perhaps, however, the relationship between the LTF and CVLM needs to be considered in a broader context. Just as Barman and Gebber and coworkers showed with respect to the LTF in the cat, it has become clear from studies in the rat and rabbit (13, 18) that the CVLM contains functionally different groups of cardiovascular neurons, including both sympathoexcitatory and sympathoinhibitory neurons. Furthermore, some sympathoinhibitory neurons in the CVLM relay baroreceptor signals to the RVLM, whereas others do not (7). In addition, there is evidence that the CVLM is a source of excitatory as well as inhibitory inputs to RVLM sympathetic premotor neurons (18). If there is some homology between the LTF in the cat and the CVLM in the rat, it might be predicted that blockade of non-NMDA receptors in the CVLM of the rat would lead to a reduction of the reflex sympathoexcitation evoked by activation of vagal afferents or peripheral chemoreceptors, as Orer et al. (20) described in the case of non-NMDA receptors in the LTF of the cat.

The suggestion that there may be some homology between the LTF in the cat and the CVLM in other species is of course highly speculative, but nevertheless may be worth testing. In addition, the alternative hypothesis that the CVLM and LTF are functionally distinct regions should also be tested. It has been shown recently that the LTF in the rat does contain neurons that have a pressor function (16), and it would be interesting to test, for example, whether blockade of non-NMDA receptors in this region in the rat has similar effects to that described by Orer et al. (20) in their study in the cat.

In any case, the excellent study by Orer et al. (20), together with previous studies from their laboratory on the role of the medullary LTF in the reflex regulation of sympathetic activity certainly suggests that the medullary pathways subserving these reflexes are more complex than the essential circuitry proposed in earlier reviews. This is not to say that these earlier representations of the reflex pathways are incorrect; instead, it is more likely that they are crucial components of a more elaborate functional organization that has so far been only partly elucidated.

ACKNOWLEDGMENT

I thank Dr. Robin McAllen for helpful discussions concerning some of the issues raised in this commentary.

REFERENCES


