Plasticity of GABA function in the nucleus tractus solitarius in hypertension

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The brain plays an important role in the normal regulation of arterial pressure, and alteration in the regulation provided by the brain may chronically influence arterial pressure leading to hypertension or hypotension. Indeed, substantial evidence suggests that human hypertension frequently has a neurogenic basis (5, 7), and certain drugs used to treat hypertension act on central neural systems controlling arterial pressure.

Experiments comparing central neural control of arterial pressure in animal models of hypertension with their normotensive controls represent a frequently used approach to study the mechanisms underlying hypertension. However, a corollary of this approach that is often overlooked is that in studying altered states of regulation, insight into the mechanisms involved in the physiological regulation of arterial pressure may be gained. Physiological control systems are often remarkably plastic and can alter their operating characteristics depending on the prevailing conditions. The study by Mei et al. (8) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology nicely illustrates this point, as their study may inform us as much about the normal control of arterial pressure as it does about hypertension.

The study by Mei et al. (8) is the most recent in a series of reports by Mifflin and colleagues (4, 13, 14) having their roots in studies we reported 15 years ago (1, 2, 9, 11). Because baroreceptor reflex regulation of the autonomic nervous system is essential for the normal control of arterial pressure and the first central synapse in this reflex arc is located in the nucleus tractus solitarius (NTS) in the dorsomedial brain stem, it is not surprising that researchers interested in the central neural control of cardiovascular function have focused on this region. In a seminal report, Doba and Reis (3) described a marked increase in arterial pressure resulting from destruction of the NTS. Because inhibition of the NTS might be analogous to its destruction and GABA is the dominant inhibitory neurotransmitter in the brain, we began to study the role GABA plays in the NTS in the regulation of arterial pressure (1). Our naive hypothesis was that enhancement of GABA-mediated inhibition of NTS function may lead to increased arterial pressure and might be a mechanism underlying at least some forms of hypertension. We demonstrated that potentiating the actions of GABA in the NTS of anesthetized rats increased arterial pressure through actions on both GABA \( \alpha \) and GABA \( \beta \) receptors (10). Furthermore, in a rat model of genetic hypertension, the spontaneously hypertensive rat (SHR), we noted that stimulation of GABA \( \beta \) receptors in the NTS, by injection of the GABA \( \beta \) agonist baclofen into the NTS, produced exaggerated increases in arterial pressure when compared to normotensive control rats (2). This observation provided some of the first evidence that cardiovascular responses elicited from the brain of SHR could be different from those of control rats and stood in marked contrast to the lack of difference in the pressor response cause by stimulation of GABA \( \alpha \) receptors in the NTS (2). The potentiated increase in arterial pressure seen in SHR in response to injection of GABA \( \beta \) agonists but not GABA \( \alpha \) agonists was one of the first demonstrations that a specific neural substrate involved in brain control of arterial pressure was altered in a model of hypertension. Subsequent studies demonstrated that potentiated pressor responses to GABA \( \beta \) agonists but not GABA \( \alpha \) agonists also occurred in other rat models of hypertension (4, 12, 13) and may occur quite quickly in response to elevated arterial pressure (13). However, the relationship of this enhanced pressor action of GABA in the NTS to specific cellular responses in the NTS remained unclear, and the relationship to the baroreceptor reflex uncertain.

Zhang and Mifflin (14) recently showed baclofen to be relatively ineffective at inhibiting baroreceptor-driven activity of NTS neurons receiving monosynaptic baroreceptor input (based on electrophysiological criteria). Baclofen does, however, inhibit the activity of neurons receiving baroreceptor input polysynaptically (14); baclofen may also act presynaptically to inhibit baroreceptor transmission (14). In contrast, the GABA \( \alpha \) agonist muscimol inhibited the activity of NTS neurons that received baroreceptor input either monosynaptically or polysynaptically (14). Mei et al. (8) now demonstrate that in a model of renal hypertension produced by removing one kidney and compressing the other, a model in which pressor responses to baclofen injected into NTS are enhanced (4, 13), neuronal responses to the iontophoretic application of GABA \( \beta \) and GABA \( \alpha \) receptor agonists are modified in a complex manner. At both 1 and 4 wk after the onset of hypertension, the effectiveness of baclofen at inhibiting aortic depressor nerve (ADN) evoked responses in NTS neurons receiving monosynaptic input was markedly increased, making it comparable to the response in the

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polysynaptic neurons. On the other hand, the effect on NTS neurons receiving polysynaptic baroreceptor input was not altered in their hypertensive rats. In contrast, the effectiveness by which muscimol inhibited ADN-evoked responses was attenuated in both groups of neurons in the hypertensive rats. Responses to GABA in general more closely resembled those of muscimol than baclofen, though at 4 wk of hypertension the neurons receiving monosynaptic input show a response to GABA that is not different from control. This response to GABA at 4 wk of hypertension possibly reflects an integration of the attenuated response to GABA_A stimulation and the potentiated response to GABA_B stimulation, although this explanation would be difficult to reconcile with the observations after 1 wk of hypertension.

These observations must be taken in the context of the potentiated pressor response to baclofen but not muscimol. As Durgam et al. (4) showed that GABA_B mRNA levels in the NTS are increased in this model of hypertension, it may be that more GABA_B receptors are made in the neurons receiving monosynaptic input from baroreceptors, thereby providing a more complete inhibition of the baroreceptor reflex and a greater increase in arterial pressure. However, this would fail to explain why the pressor response to injection of muscimol into the NTS does not change with hypertension despite the large attenuation of the effect on ADN-evoked responses. Obviously the circuitry and pharmacology of this system are extremely complex and there is much that we do not yet understand. Possibly, the key may lie in the impact of nonbarosensitive neurons, as there has been great difficulty in relating all of the data on GABA and arterial pressure regulation in the NTS to the baroreceptor reflex. In that regard, the GABA_A antagonist bicuculline injected into the NTS has only minimal effects on arterial pressure in normal rats, but markedly lowers arterial pressure in rats chronically after transection of the ADN and carotid sinus nerves (6), indicating that at least some cardiovascular responses to alteration of GABA function in NTS cannot be related to changing baroreceptor function under certain conditions.

Future studies will no doubt describe the locations of different subtypes of GABA receptors in the NTS and their roles in the regulation of arterial pressure in normotensive and hypertensive rats, and hopefully a clearer picture of their involvement will emerge. However, in the push for understanding the role GABA plays in the NTS in the pathophysiology of hypertension, we should not lose site of what such studies can tell us about physiology. The present studies provide a wonderful illustration as to how plastic these systems are. By removing one kidney and compressing the remaining kidney, possibly as a result of the ensuing increase in arterial pressure, there are marked changes in the cellular events in the NTS, and the impact of GABA on barosensitivity of different populations of neurons is changed markedly and in differing ways. Unraveling this staggering degree of complexity, and its physiological significance, in just one little part of baroreceptor reflex that is but one component of the central neural control of cardiovascular regulation, is the real challenge of future studies.

REFERENCES