Regulator of G protein signaling (RGS2)-deficient mice: a novel model to study autonomic nervous system function

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In this issue of The American Journal of Physiology: Regulatory, Integrative and Comparative Physiology, Gross and colleagues (2) present hemodynamic experiments in a novel murine knock-out model in which the gene for a regulator of G protein signaling was functionally inactivated (7). This mouse model has the potential to provide important new insights into autonomic regulation of cardiovascular function.

A variety of vasoconstrictors mediate their action on vascular smooth muscle cells (VSMCs) via receptors that are coupled to the G protein Gq. This G protein activates a signaling cascade in VSMCs that causes an increase in intracellular Ca²⁺, which ultimately elicits vasoconstriction. Regulators of G protein signaling (RGS) bind to activated Gq subunits of G proteins and markedly stimulate their GTPase activity. This deactivates and terminates downstream signaling (5).

RGS2 is one of over 30 known RGS. Due to three unique residues within the G protein-binding domain of RGS2 it is selective for inhibition of Gqα (3). In 2000, Oliveira-dos-Santos and colleagues (7) engineered mice with target mutation of RGS2. Because RGS2 inhibits Gq proteins that are coupled to receptors that mediate VSMC constriction, it is reasonable to assume that blood pressure in mice that lack the inhibitory action of RGS2 is elevated. Indeed, hypertension has been reported in heterozygous and homozygous RGS2 knockout mice (4). These mice also exhibit renovascular abnormalities, persistent constriction of the resistance vasculature, and prolonged responses to vasoconstrictors in vivo (4). Therefore, this mouse model may be extremely useful to study regulation of vascular function via vasoconstrictors that depend on Gq protein-coupled receptors, such as ANG II, endothelin, vasopressin, and norepinephrine.

Because RGS2 is also expressed in the brain, Gross et al. hypothesized that central nervous system mechanisms may contribute to hypertension in RGS2−/− mice. Especially, an increase in sympathetic nervous system activity and/or altered baroreflex-mediated sympathetic and parasympathetic control of cardiovascular function may add to the elevated blood pressure of RGS2−/− mice (4). To test this hypothesis, they performed a series of hemodynamic experiments in RGS2−/− and RGS2+/+ control mice that were instrumented with telemetric blood pressure sensors. Using this approach, they could demonstrate for the first time that circadian blood pressure and heart rate rhythms are maintained in hypertensive RGS2−/− mice. This mouse model may be extremely useful to study regulation of vascular function via vasoconstrictors that depend on Gq protein-coupled receptors, such as ANG II, endothelin, vasopressin, and norepinephrine.

Several of their findings indicate elevated sympathetic outflow to the periphery in RGS2−/− mice. First, urinary norepinephrine concentration and daily urinary norepinephrine excretion were significantly elevated in the knockout mice compared with wild-type controls. Second, there was a larger decrease in blood pressure in response to intraperitoneal administration of a low dose of the α₁-adrenergic receptor antagonist prazosin. Third, the blood pressure response to behavioral stress declined at a slower rate in RGS2−/− mice. However, other results of their study indicate that sympathetic nervous system activity is not increased in RGS2−/− mice compared with wild-type mice. The blood pressure fall in response to higher doses of prazosin was similar in both strains of mice, ganglionic blockade with hexamethonium did not reduce blood pressure or heart rate in the knockout mice, the heart rate response to β₁-adrenergic receptor blockade was similar in both strains, and spectral analysis of arterial blood pressure and heart rate did not reveal increased low frequency spectral power that is thought to reflect sympathetic modulation of vascular tone and heart rate, respectively (1, 6). Due to these conflicting data, the authors state their final conclusion cautiously: “The increase in blood pressure in RGS2−/− mice is not solely explained by peripheral vascular mechanisms. A central nervous system mechanism might be implicated by an increased sympathetic tone” (2). As the authors further emphasize, “further direct measurements (of sympathetic nervous system activity) will be necessary to test this notion.”

The authors also investigated a possible contribution of alterations in baroreceptor reflex function to the elevated blood pressure in RGS2−/− mice. Using a cross-spectral analysis approach, baroreflex sensitivity was not found to be different in both strains of mice. However, the data indicate a resetting of the reflex to higher blood pressure values in the knockout mice. The question if this resetting of the baroreflex is secondary to the elevated blood pressure or primarily contributes to hypertension in this animal model deserves further investigation.

Another exciting question is how sympathetic modulation of vascular tone is altered in RGS2−/− mice. As mentioned previously, in vivo responses to vasoconstrictors are prolonged in mice with target mutation of RGS2 (4). Therefore, one would expect a more sluggish vascular response to sympathetic stimuli. Indeed, the blood pressure response to behavioral stress declined at a slower rate in RGS2−/− mice in the study by Gross et al. (2). If the vasculature responds more sluggishly to sympathetic inputs, one might further speculate that sympathetic modulation of vascular tone causes blood pressure fluctuations at lower frequencies in RGS2−/− mice compared with wild-type mice. Maybe this mechanism explains why Gross and colleagues did not find a significant increase in low-frequency spectral power of arterial blood pressure and heart rate.

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rate in RGS2−/− mice (2). Maybe one has to look at frequencies below the traditional low-frequency range to identify sympathetic modulation of vascular tone in RGS2−/− mice. With this regard it is interesting to note that the frequency at which sympathetic modulation of vascular tone is most effective varies among different vascular beds. In the mesenteric circulation of rats, sympathetic modulation of vascular tone is most effective at frequencies between 0.2 and 0.5 Hz (9,10), while it is most effective below 0.1 Hz in the cutaneous circulation in the same species (11). One may speculate that differential expression of RGS2 affects the frequency response characteristic of sympathetic modulation of vascular tone in different vascular beds.

Taken together, the study by Gross et al. (2) contributes considerably to our understanding of blood pressure regulation. G protein-coupled receptors appear to be highly regulated, and alterations of this regulation can lead to diseases such as hypertension. Additional studies are needed to further elucidate the contribution of central nervous system effects of regulators of G protein signaling (RGS). The RGS2−/− mouse model is a promising tool to perform these studies.

REFERENCES


