Letters to the Editor

The Role of the α1B-Adrenergic Receptor in Vascular Structure and Function

To the Editor: Townsend et al provide interesting subplots to the perplexing issue of the role of α1b-adrenoceptors (ARs) in cardiovascular regulation.

The physiological role of this receptor is unclear because it has no universally acknowledged selective antagonists. This accentuates use of the α1b-knockout (KO) mouse and raises 2 sets of issues: (1) tissue distribution, and (2) developmental compensation.

First, Townsend et al’s interpretation of the attenuation found in the baroreceptor reflex of the α1b-KO mouse does not take account of the widespread distribution of the receptor in the central nervous system related to autonomic regulation. There is no more evidence for the loss of reflex being at the level of the heart than in the brain. Indeed, the statistically significant loss of the heart rate reflex would support the latter (admittedly, numerically trivial because heart rate is already maximal). More significant, if the cardiac role of α1b is “likely to be modest and secondary to β-ARs,” perhaps this also suggests that the heart is not the site of this action.

Second, the lack of selective antagonists limits interpretation of vascular phenotypes of the α1b-KO mouse. This strain does not show substantial changes from normal across a range of different arteries. In all arteries tested, there were subtle changes in the pharmacological data indicating that loss of α1b-AR changed the properties of the other receptors. In the small mesenteric arteries used by Townsend et al, antagonists indicate mainly α1a-AR in contraction. However, in the α1b-KO mouse, this vessel loses the ability to remodel in noradrenaline-induced hypertension. Together, we hypothesize that in most arteries, the α1b-AR exerts a regulatory role rather than being directly involved in contraction.

Regarding the loss of a prazosin-sensitive, nerve-induced contraction in mesenteric arteries, we would suggest that the concentration used (10 μmol/L) is not specific. It also seems unlikely that the neurotransmitter would not activate other subtypes that are present. We reported previously a similar phenotype in this strain.

In tail artery, the α1b-KO mouse has a significantly slower contractile response to periarterial nerve stimulation than the α1a-AR subtype by neurotransmitter noradrenaline. This was doubly interesting because our original suggestion of subtypes of α1-AR was partly based on α1b-ARs preferentially releasing intracellular calcium stores, thereby inducing the initial rapid contraction phase in blood vessels. We also found a reduction in the number of adventitial fibroblasts in the α1b-KO mouse tail artery. We now interpret this as evidence of the loss of a developmental influence of α1b-AR, with multiple consequences for vascular activation.

The debate on junctional and extrajunctional receptors in arteries goes back a long way, traditionally on the basis of the failure of some drugs to block responses. Townsend et al’s observations reactivate this, and our perhaps perverse interpretation turns this around so that we suggest that the loss of a response by eliminating a receptor does not necessarily imply that the receptor is involved acutely in the response.

Response

We greatly appreciate the comments of Drs Daly and McGrath regarding our work and will attempt to respond to each comment in turn.

First, the point regarding the possibility that the attenuated baroreflex responses observed may be a function of central adrenergic dysregulation in the α1b-adrenergic receptor (AR) knockout (KO) mice is well taken. We certainly provide no evidence that there is unaltered sympathetic nervous system activity in the KO mice. However, in our article, we make reference to a body of work in which monoamine concentrations in the brain of KO mice were measured and shown to be no different from those of wild-type (WT) mice, suggesting that a central mechanism explaining the effect is unlikely.

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4. Daly CJ, Cotecchia S, McGrath JC. Low frequency electrical field stimulation elicits responses in segments of mouse tail artery which are slower in α1B-knockout mice than in control mice. Fifth Internet World Congress for Biomedical Sciences. Naunyn-Schmiedeberg’s Arch Pharmacol. 1998;358:P6.40.


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α1B-AR may be important in the remodeling process in the heart and vessels as proposed by Daly and McGrath. The dilemma as to whether effects in vivo are attributable to abnormal central aberrant sympathetic signaling or peripheral end-organ responses awaits the measurement of an end point such as renal sympathetic nerve activity, a technique that we continue to explore with our collaborators.

With regard to the responses to the exogenous administration of agonists to blood vessels, our findings are completely consistent with the findings of Daly and McGrath’s elegant study4 (ie, no or very subtle differences in the responses in a number of different vascular beds). It is with regard to the responses to endogenously released norepinephrine (NE) that our interpretation of the data differ. With regard to the loss of prazosin-sensitive nerve-induced contraction in mesenteric arteries, Daly and McGrath suggest that the concentration of prazosin used (10 mmol/L) is nonspecific. Although the Ki of prazosin for the α1-AR is ~0.1 to 1 nmol/L in binding assays, the majority of experiments in in vitro bioassays use concentrations well in excess of this.5 We used a concentration of prazosin that was 10-fold lower than those published in our manuscript and have observed the same responses. Furthermore, the fact that the responses at 2Hz are not significantly different between WT and KO mice does not suggest activation of the α1B-AR, but rather, the rapid activation of nonadrenergic receptors (specifically purinergic receptors activated by ATP) that are coreleased with NE in response to sympathetic nervous system activation. These findings are in agreement with others that demonstrate a predominant response mediated at lower frequency cotransmitters other than NE.6,7 With regard to the suggestion that it is unlikely that the released neurotransmitter would not activate other receptor subtypes, we would have to respectfully disagree. One of the emerging paradigms in the biology of this decade is the concept of special confinement of signaling. The classic concept of specific neuroeffector signaling finds its origins in the neuromuscular junction, where specific nicotinic cholinergic receptor subtypes are localized to the motor end plate, whereas other receptor subtypes are expressed in extrajunctional regions.8 This ensures that receptor subtypes transduce focused signals in a distinct and sometimes directionally opposite manner in the same tissue or cell. Furthermore, the expression and compartmentalization of these receptor subtypes are driven by release of neuregulins (trophic peptides), which ensure this association between nerve and postjunctional receptor.9

In conclusion, we believe we have much to learn regarding α1C-AR subtype function and dysfunction in the circulation, particularly as they relate to neuroeffector signaling in the vessels and heart. We look forward to an ongoing investigation and lively discussion as to their roles.

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The Role of the \( \alpha_{1B} \)-Adrenergic Receptor in Vascular Structure and Function
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