Letters to the Editor

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Neuropeptide Y and Sympathetic Nervous System in Blood Pressure Regulation

To the Editor:

We read with great interest the recent article by Dr Michalkiewicz and his colleagues deals with a possible link between neuropeptide Y (NPY) and sympathetic nervous system in the NPY-transgenic rats. The results of their presented study demonstrated that overexpression of endogenous NPY in the transgenic rats was associated with lower blood pressure in baseline and during stress. Dr Michalkiewicz proposed that the antiadrenergic action of NPY within the sympathetic nervous system may protect the cardiovascular system from excessive adrenergic excitations.

Several studies have reported the influences of NPY on sympathetic neurotransmission in both the central and peripheral nervous systems. In a study we presented earlier, the change in norepinephrine (NE) release induced by NPY was investigated in rat hypothalamus and medulla oblongata. In an in vitro study using rat brain slices, we showed that NPY inhibited the stimulation-evoked NE release in a dose-dependent manner. It was also demonstrated that NPY potentiated the inhibitory effect of the α2-adrenergic receptor agonists on NE release. In contrast, blockade of the α2-adrenergic receptors or pretreatment of pertussis toxin (a potent inhibitor of the Gi-proteins) diminished the inhibitory effects of NPY on NE release. It would be possible that NPY might reduce NE release in the central nervous system partially mediated by the α2-adrenergic receptors and the pertussis toxin-sensitive Gi-proteins. In addition, the inhibitory effect of NPY on NE release was impaired in spontaneously hypertensive rats (SHR).

It was reported that NPY increased the number of the α2-adrenergic receptor binding sites in medulla oblongata of normotensive Wistar-Kyoto rats, whereas NPY failed to increase the number of α2-adrenergic binding sites in membranes of medulla oblongata of the spontaneously hypertensive rat. This suggests that the interactions between NPY and α2-adrenergic receptors might be disturbed in hypertension.

In the separate series of the experiments, Dr Michalkiewicz showed that the pressor responses to exogenous NE were significantly increased in the NPY-transgenic rats. The finding might be consistent with the hypothesis that genetic upregulation of NPY could enhance the α2-adrenergic receptor sensitivity. Therefore, we would like to know whether the α2-adrenergic receptor function might be altered in the NPY-transgenic rats. In this context, it can be speculated that, because central stimulation of the α2-adrenergic receptors might markedly reduce blood pressure, the changes in the α2-adrenergic receptors might partially explain the blood pressure-lowering effect of NPY in this type of transgenic rats. Further studies should be performed to assess more thoroughly the relationships between NPY and sympathetic nervous system and their role in the blood pressure regulation.

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Response: Hypotension and Reduced Catecholamines in Neuropeptide Y Transgenic Rats

We appreciate Dr Tsuda’s interest and enriching comments regarding our recent published paper. The correspondent’s comments are very insightful and point to the α2-adrenergic signaling as the most likely mechanism of the hypotensive and sympatholytic effects of the genetic upregulation of neuropeptide Y (NPY). Indeed NPY appears as a potent presynaptic inhibitor of norepinephrine (NE) release in the brain centers involved in regulation of blood pressure. This suggestion is supported by Dr Tsuda’s own extensive work assessing the physiological importance of functional cooperation between endogenous NPY and NE in the sympathetic nervous system. This notion is also in line with the findings of others. It is important to emphasize that our observations of the sympatholytic and hypotensive effects of long-term genetic upregulation of NPY in transgenic rat are in agreement with the correspondent’s findings obtained by using isolated cerebral slices models. Unfortunately, the stated space limitations of the journal did not allow us to discuss all of his interesting and very relevant findings more extensively in our report.

We entirely agree with Dr Tsuda’s suggestion that this transgenic rat provides a unique model to determine the physiological importance of functional cooperation between endogenous NPY and NE in the sympathetic nervous system. In particular, this transgenic rat will allow us to determine whether the hypotensive responses to increased NPY signaling are a consequence of enhanced α2-adrenergic functions. It is particularly difficult to determine such interreceptor interactions using a short-term model. Therefore, availability of a genetic model allowing long-term, whole-animal manipulation is advantageous. Indeed, there are data to suggest the importance of endogenous NPY in regulation of the function of the α2-adrenoceptor. Like the α2-agonist clonidine, NPY inhibits NE release in synapses from the medulla oblongata, and it potentiates clonidine-induced inhibition of NE release. Along with hypotension, stimulation of the central α2-adrenoceptor leads to sedation. We have reported anxiolysis and behavioral insensitivity to
restraint stress in this transgenic rat. This peptide has also been suggested to be involved in the enhanced stress resilience in humans. These anxiolytic effects of NPY could reflect an enhanced α2-adrenoceptor signaling due to NPY upregulation. Thus, indeed, as the correspondent suggests, NPY transgenic rat provides an appropriate model to study the modulatory role of NPY in the regulation of adrenergic signaling.

In summary, we agree with Dr Tsuda that NPY appears as an important endogenous modulator of the α2-adrenoceptor and that NPY transgenic rat provides a useful model to assess many functional aspects of the interactions between NPY and the α2-adrenergic signaling implicated in the regulation of blood pressure by the sympathetic nervous system.

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