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Role of catecholamine-induced activation of vagal afferent pathways in regulation of sympathoadrenal system activity: negative feedback loop of stress response

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Stress-induced activation of the hypothalamic-pituitary-adrenal axis and sympathoadrenal system is precisely regulated by well-documented negative feedback mechanisms. These include direct negative feedback effect of glucocorticoids on brain structures regulating the hypothalamic-pituitary-adrenal axis activity. However, since the blood-brain-barrier is impermeable to circulating catecholamines, the role of circulating epinephrine and norepinephrine in feedback regulation of the sympathoadrenal system activity is unclear. Here we show that vagal innervation of the adrenal medulla combined with the presence of β-adrenergic receptors on vagal sensory neurons, the epinephrine-induced activation of vagal afferents, and increased plasma epinephrine levels following subdiaphragmatic vagotomy indicate that sensory fibers of the vagus nerve participate in the monitoring of plasma and tissue catecholamine concentrations. Furthermore, it shows that signaling transmitted by vagal afferents regulates sympathoadrenal system activity at the level of the brain. Therefore, we propose that vagal sensory fibers, directly activated by epinephrine and norepinephrine, represent the afferent limb of a negative feedback loop that adjusts the activity of the sympathoadrenal system according to actual plasma and tissue catecholamine levels.

Key words: adrenal medulla, catecholamines, hypothalamic-pituitary-adrenal axis, stress, sympathoadrenal system, vagus nerve.

Exposure of higher organisms to stressors is accompanied by activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathoadrenal system (SAS), the two principal systems controlling stress responses. Mobilization of energetic resources and increased alertness as a consequence of HPA axis and SAS activation is essential for an organism to overcome stressful situations (Ulrich-Lai and Herman 2009). However, excessive or inadequate basal activity and responsiveness of the HPA axis and SAS can impair growth, development, metabolism, and behavior, as well as participate in the development of various acute and chronic diseases (de Kloet et al. 2005; Chrousos 2009). Therefore, under physiological conditions stress-induced activation of both the HPA axis and SAS is precisely regulated by negative feedback mechanisms similar to those used by other regulatory systems (Rodrigues et al. 2009). Negative feedback regulation of the HPA axis mediated by direct glucocorticoids effect on brain structures is well documented. Glucocorticoids pass through blood-brain-barrier and modulate activity of HPA axis through suppression of release of corticotrophin releasing factor by paraventricular hypothalamic neurons. Thus, activation of HPA axis induces increase of circulating glucocorticoids that in turn as a part of negative feedback loop regulate HPA axis activity (Lightman et al. 2002).

Unlike the HPA axis, the mechanisms underlying negative feedback regulation of SAS activity by peripheral catecholamines have only recently been to be elucidated. Because the blood-brain-barrier is imper-

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meable to circulating epinephrine and norepinephrine (Hardebo and Owman 1980), plasma catecholamines cannot directly influence brain structures involved in regulating SAS activity. Therefore, the central effect of plasma catecholamines on the SAS must be somehow mediated via mechanisms that transmit signals related to plasma epinephrine and norepinephrine concentrations to the brain. While circulating catecholamines may potentially influence brain structures at the level of circumventricular organs (Kostrzewa 2007), the accumulated evidence suggest that peripherally released epinephrine and norepinephrine modulate SAS activity via the activation of vagal afferent pathways.

Sensory vagal pathways as a part of negative feedback loop regulating sympathoadrenal system activity

We suggest that sensory pathways of the vagus nerve monitor plasma and tissue catecholamine levels, thereby serving as an afferent part of any feedback loop regulating the activity of the SAS in accordance with directly monitoring peripheral catecholamine levels. Therefore, these afferent vagal pathways may represent a "brake" for the SAS system during situations associated with increased activity of sympathetic nerves and the adrenal medulla, such as during the response to a stressor. Activation of this "vagal brake" may be induced by the occupation of β-adrenergic receptors localized on vagal sensory endings within several organs (e.g. adrenal medulla, heart, liver) by circulating and tissue catecholamines.

The existence of such a "vagal brake", directly activated by catecholamines released from the adrenal medulla and sympathetic nerve endings is supported by several findings. First, vagal sensory nerves innervate a broad spectrum of organs with direct exposure to plasma epinephrine and norepinephrine (Miyashita and Williams 2006). For example, the adrenal medulla, the main source of circulating epinephrine, is innervated by vagal sensory fibers as demonstrated by the observation that application of a retrograde tracer into the adrenal medulla of rats and guinea-pigs results in the labeling of neurons within vagal sensory ganglia (Coupland et al. 1989).

Vagal sensory neurons express adrenergic receptors. Specifically, an *in vitro* study has demonstrated that the vagal (nodose) ganglia of both rats and human posses adrenergic receptors, predominantly of the β_2-adrenoreceptor subtype. Furthermore, unilateral vagal ligation induces an accumulation of adrenergic receptors adjacent to the ligature sites, indicating axonal transport of adrenergic receptors along the vagus nerve (Lawrence et al. 1995), while unilateral cervical vagotomy in rats enhances norepinephrine-induced activation of left nodose ganglion neurons. This phenomenon is in accordance with observations noting the up-regulation of α-adrenergic receptor mRNA in nodose ganglion located upstream of a vagotomy (Huang et al. 2004). Furthermore, administration of the β-adrenoreceptor agonist isoprenaline for 14 days results in the down-regulation of adrenergic receptors within the nodose ganglia (Watkins et al. 1996). These findings may reflect adaptive responses by the vagal sensory neurons responsible for monitoring plasma and tissue catecholamine levels. Whether or not the long-term elevation of plasma catecholamine levels induced by exposing an organism to stressors elicits a similar effect needs further investigation.

Catecholamines increase the activity of vagal afferent pathways. For example, local application of norepinephrine to the isolated aortic arc of rats produces an excitatory response within the aortic baroreceptor fibers of the vagus nerve. It is suggest that this excitatory action of norepinephrine is independent of smooth muscle activity and is mediated by α_1-adrenergic receptors located on aortic baroreceptor nerve endings (Goldman and Saum 1984). It is known that intraperitoneal administration of epinephrine induces significant increases in the firing of vagal afferent fibers in rats. However, when these rats were pretreated by a peripherally acting β-adrenoreceptor antagonist (sotalol), the excitatory action of epinephrine was eliminated (Miyashita and Williams 2006). Findings from *in vitro* preparations of vagus nerve fibers disconnected from the heart and other peripheral organs indicate there is also a direct effect of catecholamines on afferent vagal activity. For example, application of the selective β-adrenoreceptor agonist isoproterenol to isolated sections of the vagus nerve significantly increases intracellular cAMP levels (Miyashita and Williams 2006; Schreurs et al. 1986). Moreover, the direct effect of catecholamines on vagal sensory pathway activity indicates that there may be an epinephrine-sensitizing effect affecting vagal chemosensitive neurons mediated by the activation of β_3-adrenoreceptors and the intracellular cAMP-PKA signaling cascade (Gu et al. 2007).

Transection of the vagus nerve is accompanied by significant increases in SAS activity as demonstrated by the increase in plasma epinephrine seen 3, 7, and 14 days following subdiaphragmatic vagotomy in rats

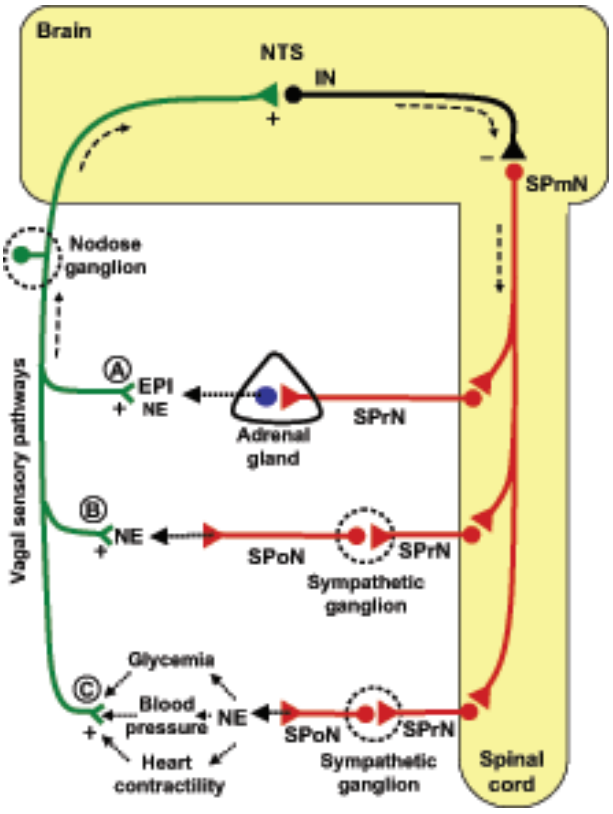

Fig. 1. Proposed mechanisms of a "vagal brake" of sympathoadrenal system activity based on the monitoring of plasma and tissue catecholamine levels by vagal sensory nerve endings.

Adrenergic receptors of vagal sensory nerve endings are exposed to both circulating and tissue epinephrine (EPI) and norepinephrine (NE) released from the adrenal medulla (A) and sympathetic nerve endings (B). This activation of adrenoreceptors on vagal sensory nerve endings increases the activity of vagal afferent pathways, which in turn inhibit the activity of sympathetic premotor neurons (SPmN) via interneurons (IN) within the nucleus tractus solitarii (NTS). The resulting increases in catecholamine concentrations in the periphery of an organism lead to the inhibition of activity of sympathetic preganglionic neurons (SPrN) and a consequence, decreased release of EPI and NE from adrenal medulla and sympathetic postganglionic neurons (SPoN). However, vagal afferent nerves may be activated by catecholamines indirectly as well (C) as peripherally released catecholamines alter the activity of internal organs (e.g. increase of heart contractility, blood pressure, and glycemia) and these changes stimulate mechanosensitive and chemosensitive nerve endings of the vagus nerve leading to increased vagal afferents activity.

when compared to sham operated animals (Khasar et al. 2003). This indicates that transection of the afferent part of this negative feedback loop results in an exaggerated activation of the SAS. Unfortunately, we are unaware of any studies demonstrating the effect of subdiaphragmatic vagotomy on plasma norepinephrine levels. However, it would be interesting to investigate the effect of vagotomy on catecholamine release during exposure to stressors. It is known that hepatic vagotomy in rats does not affect plasma catecholamine levels during exposure to a physical load compared to controls (Latour et al. 1995). Therefore, it is possible that other vagal branches are responsible for monitoring plasma and tissue catecholamine levels, most probably those innervating the adrenal medulla.

The findings mentioned above indicate that afferent sensory fibers of the vagus nerve monitor plasma and tissue concentrations of epinephrine and norepinephrine and then transmit this information as to modulate activity of the SAS. However, it is important to note that afferent vagal pathways can transmit a wide range of signals (Janig 2006) including some influenced by catecholamines released from the adrenal medulla and sympathetic nerve endings (Young and Landsberg 1998). Therefore, this "vagal brake" may also be indirectly activated by increased levels of peripheral catecholamines via activation of one or more of the other receptors localized to vagal sensory endings as a consequence of other catecholamine-induced responses. As a result, it is important to clarify whether activation of afferent vagal pathways during stress is a consequence of direct activation of β-adrenergic receptors on vagal sensory endings by circulating and tissue catecholamines, or whether increased activity of vagal afferents is mediated by activation of other types of receptors including gluco- and mechanoreceptors known to be localized on vagal sensory endings responding to catecholamine-induced changes in the internal environment (Fig. 1).

Conclusions

The activity of the SAS is regulated by several mechanisms involving both central and peripheral interactions with the parasympathetic nervous system (Ondicova and Mravec 2010). The accumulated evidence indicates that afferent vagal pathways monitor plasma and tissue catecholamine levels and modulate the activity of sympathetic preganglionic neurons in a manner reflecting the activity of the SAS. Based on the above-mentioned data, we suggest that sensory vagal pathways represent a crucial part of the afferent negative feedback loop regulating the activity of the SAS. This mechanism may even represent the principal negative feedback mechanism for regulating stress response.

Exposure to stressors leads to activation of the SAS and increases in plasma and tissue catecholamine levels. This released epinephrine and norepinephrine binds to adrenoreceptors on vagal sensory nerve endings, thereby increasing the activity of vagal afferent pathways. Consequently, vagal afferents activate neurons of the nucleus tractus solitarii, the main relay structure processing visceral information. Neurons of nucleus tractus solitarius then use this information to inhibit stress responses through modulation of forebrain and brainstem structures participating in the regulation of SAS activity. This way, stress-induced activation of the SAS leads to the release of catecholamines, which then elicit a variety of peripheral effects. Signals related to these effects are then fed back into the SAS where they further modulate stress responses. We suggest that the negative feedback regulation of SAS activity also involves vagal afferent pathways directly monitoring levels of peripherally released catecholamines (Fig. 1).

Alteration of transmission of signals related to plasma and tissue catecholamine levels via the vagus nerve may lead to inappropriate, exaggerated activation of the SAS during both basal and stress induced conditions. Pharmacological and electrical stimulatory interventions focused on modulating the transmission of signals by vagal pathways participating in the monitoring of peripheral catecholamine levels may represent a new tool for the treatment of diseases characterized by inappropriate SAS activation (e.g. essential hypertension, heart failure, anxiety).

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