A Novel Top-down Strategy For Addressing Autonomic Imbalances

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ABSTRACT

All involuntary bodily functions are controlled by the autonomic nervous system (ANS). Because of its extensive influence, when the ANS is out of balance, it can cause a range of health issues involving sleep quality, energy levels, metabolism, gastrointestinal and cardiovascular function, and more. ANS imbalances manifest differently with each patient due to genetic predisposition and numerous other factors. Strides in the elucidation of neurocircuitry have demonstrated that neurotransmitter-based activity in certain regions of the brain directly and indirectly influence ANS function. This paper discusses the relevant neurocircuitry and clinical support for ANS imbalances.

Introduction

The nervous system is comprised of the central and the peripheral arms. Within the peripheral arm, the autonomic nervous system (ANS) governs all involuntary biological processes. The ANS is itself comprised of two branches – the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). During waking hours, and particularly in stress situations, it is the SNS that is primarily active and is responsible for the "fight or flight" stress response. The PNS is more active at night and in non-stress settings, and controls "rest and digest" functions. The balance between the SNS and PNS is crucial for maintaining homeostasis and overall health.

Because of the ANS's extensive influence on physiology, ANS dysregulation can lead to many common health complaints such as fatigue, sleep disturbances, and metabolic issues. Consequently, many prestigious health institutions have come to recognize and endorse the importance of ANS assessment, including the American Heart Association and the National Institutes of Health.

Some more commonly used clinical assessments of the ANS include heart rate variability, respiratory analysis, and the Valsalva maneuver. Less common and more complex assessments of the ANS include quantitative sudomotor axon reflex test (QSART), silastic sweat imprint, and thermoregulatory sweat test (TST). These approaches, which can require costly instrumentation, have limited clinical relevance due to their inability to pinpoint the biochemical nature of ANS imbalance.

Advances in ANS Testing

Limitations in traditional autonomic testing can be overcome by assessing peripheral neurotransmitters in biofluids such as urine. Neurotransmitters, which relay information within and from the nervous system, are useful indicators of ANS function. For over a decade, NeuroScience, Inc. has offered urinary neurotransmitter testing as a valuable tool for healthcare practitioners to assess and address their patients' health concerns. When the results of such testing indicate neurotransmitter imbalances, it is tempting to interpret the results based solely on excitatory and inhibitory neurotransmitter imbalances. However, at a deeper level, the neurotransmitter imbalances reflect abnormalities in the *tone* or "regular idling" activity of the various branches of the nervous system, specifically the ANS.

Neurocircuitry in Action

The tone of the ANS has a major impact on organ system activity, and is reflected in the peripheral neurotransmitters. If a person's SNS is operating at a suboptimal level (in other words, the individual has low sympathetic tone), it is common to see a correspondingly reduced level of certain peripheral neurotransmitters such as norepinephrine. Conversely, an increase in sympathetic tone results in elevated levels of these same peripheral neurotransmitters.

Advances in neurocircuitry research have afforded a better understanding of the psychological and pathophysiological effects of stressors, both exogenous and endogenous. For example, investigations have uncovered the role of the central nervous system in the control of the hypothalamic pituitary adrenal (HPA) axis during stress (Herman et al., 2008; Herman & Cullinan, 1997; Zhong et al., 2008; Zeigler et al., 2005).

Similarly, neurocircuitry insights have revealed that ANS dysregulation can often be traced to alterations in key areas of the brain that maintain balance between SNS and PNS tone (Lechin et al., 2009; Sun, 1995). This helps explain why some patients' symptoms do not always respond to interventions that merely increase a depleted peripheral neurotransmitter or lower an elevated one. Such approaches are, at best, short-term solutions that help stabilize the ANS, but fail to address the central (neurocircuitry) issue(s).

Investigations have found that a number of common health concerns (e.g. low mood, sleep difficulties) can be successfully addressed by targeting specific brain nuclei with the therapeutic guidance of neurotransmitter and metabolite testing in urine and blood (Lechin et al., 1996). In other words, ANS imbalances, while impacting peripheral organ systems and tissues, are likely governed by central brain regions. The following examples describe two opposing profiles of ANS imbalance and their neurocircuitry explanations.

- *Low urinary norepinephrine combined with elevated cortisol and epinephrine* – This imbalance may result from upregulated activity of specific brainstem regions including the serotonergic dorsal raphe (DR), noradrenergic locus ceruleus (LC), and adrenergic rostroventral lateral medulla (C1) (See Fig. 1, middle panel). The C1 is known to trigger the release of epinephrine and cortisol from the adrenal medulla into the circulation (Lechin & van der Dijs, 2008). Increased activity of these brainstem nuclei has an opposing effect on the noradrenergic A5 area (Fig. 1).
- *Elevated urinary norepinephrine relative to cortisol and epinephrine* - This profile may be due to upregulated activity of the serotonergic median raphe (MR) and noradrenergic A5, resulting in decreased activity of the LC, C1, and DR (Fig. 1, lower panel). Neurons in the A5 area project to the lumbar spinal segment where preganglionic sympathetic nerves are stimulated to release norepinephrine into the circulation. Furthermore, noradrenergic sympathetic nerves that innervate the adrenal gland may decrease the release of epinephrine and cortisol by acting on inhibitory alpha-2 adrenergic receptors (Lechin & van der Dijs, 2008).

In summary, several brain areas, in particular the noradrenergic LC, are critical for maintaining balance between nuclei, notably the C1 and A5, that have opposing influences on ANS function. Disturbances influencing any one of these brain regions can lead to ANS imbalances. For example, research has suggested a potential involvement of the locus ceruleus-noradrenergic system in conditions involving excessive energy and difficulty with focus. The noradrenergic LC is integral in modulating attention and behavioral-related processes. It has been demonstrated that patients with this condition often have low levels of norepinephrine. Not surprisingly, interventions that enhance noradrenergic neurotransmission are commonly recommended to modulate attention and behavioral-related processes (Berridge et al, 2003).

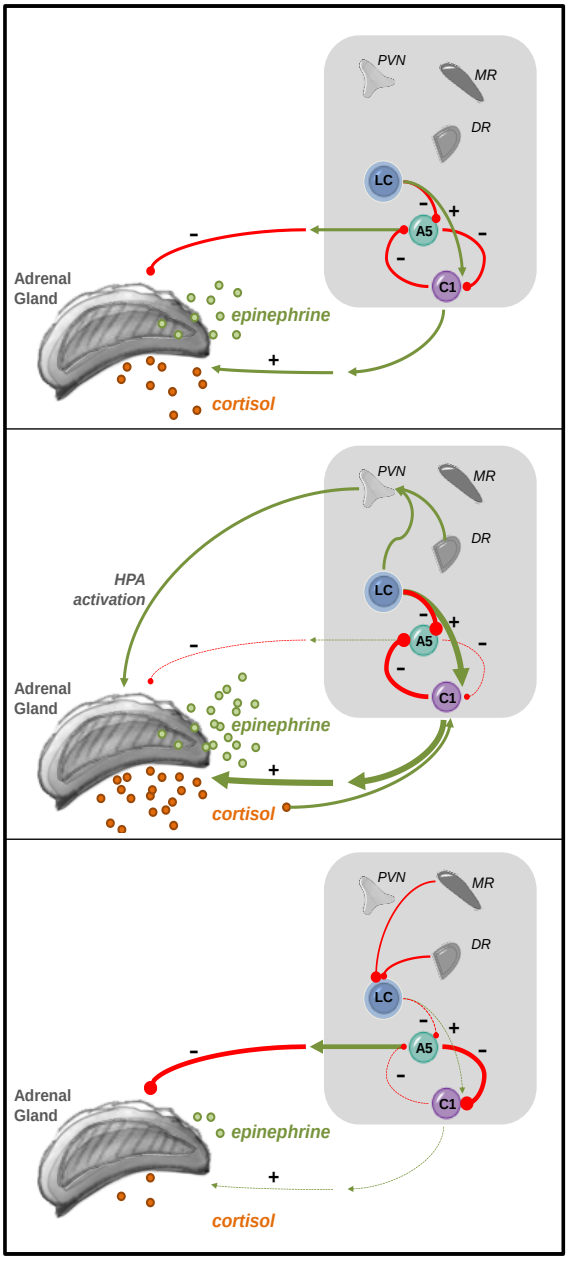

Figure 1. The balance between adrenal and neural sympathetic nervous system activity depends on the balanced interplay of key nuclei in the brainstem, particularly the locus ceruleus (LC), rostral ventral lateral medulla (C1) and fifth arcuate nucleaus (A5) *(top panel)*. Additional nuclei such as the dorsal raphe (DR), median raphe (MR), and paraventricular nucleus (PVN) further modulate the function of the LC. Chronic stress or aging can shift the balance of these signals, resulting in adrenal sympathetic overactivity *(middle panel)* or neural sympathetic overactivity *(lower panel)*.

This highlights the importance of addressing central (brain) levels of norepinephrine to bring about a more balanced ANS and relieving a plurality of associated symptoms.

Targeted Therapeutic Interventions

ANS imbalances identified by urinary neurotransmitter testing frequently present with multiple abnormal findings. Addressing each neurotransmitter biomarker singly could translate into in treatments with five or more medications and/ or supplements. On the other hand, with the insight that central brain regions can influence ANS function, a "top-down" approach directed at these central control systems is likely to address multiple symptoms with a shared root cause, therefore reducing the number of interventions while improving response rates.

In order to address an ANS imbalance reflected in *low urinary norepinephrine combined with elevated cortisol and epinephrine*, L-tyrosine ethyl ester (TEE) can be used to boost low noradrenergic sympathetic (SNS) activity. Tyrosine is an amino acid precursor for the synthesis of the catecholamines epinephrine, norepinephrine, and dopamine (Topall, 1989). Supporting norepinephrine in particular can help provide healthy energy levels, as well as a positive mood and mental clarity. TEE differs from traditional amino acid-based supplements in that its esterification vastly increases absorption as well as bioavailability; L-tyrosine esters are more lipophilic and are absorbed up to ten times faster than traditional L-tyrosine (Reitveld, 2011). Because esterified forms of tyrosine can cross the blood- brain barrier (Topall, 1989), TEE is likely to support norepinephrine and increase SNS tone by promoting central noradrenergic signaling, specifically the largest noradrenergic nucleus in the brain, the LC.

As an adjunct to TEE, L-glutamic acid has been demonstrated to increase circulating norepinephrine levels and support peripheral SNS activity (Lechin, 2010), making it an ideal ingredient for individuals with elevated adrenal function (manifested by increased cortisol and/or epinephrine). L-glutamic acid stimulates vagal afferent signaling to the brain to increase SNS activity, enhancing mental energy and countering daytime fatigue (Kondoh, et al., 2009). Small oral doses of L-glutamic acid were found to preferentially stimulate the A5 area of the brain but not the C1 or the LC (Lechin, 2010).

Additional ingredients that support catecholamine levels can complement the effect of TEE and glutamic acid and maintaining a balance between PNS and SNS.

- L-DOPA is an amino acid precursor of dopamine, norepinephrine, and epinephrine (Mena et al., 2009), the administration of which is associated with enhanced energy and positive mood.
- Diosmin is a naturally derived, well-tolerated flavonoid glycoside found in many citrus fruits. It inhibits the enzyme catechol-O-methyl transferase (COMT), which normally degrades norepinephrine. Inhibition of this enzyme therefore maintains norepinephrine levels which consequently support sympathetic activity (Boudet, 1986).

Furthermore, 5-HTP is useful not only in supporting serotonergic signaling by the DR and MR in the brainstem, but also provides support for serotonin which can sometimes become modestly suppressed in the face of strong catecholamine support. Finally, L-arginine can help lower epinephrine and elevate serotonin. In addition, arginine is broken down into nitric oxide, which promotes parasympathetic nervous system activity and therefore supports the balance between the SNS and PNS branches of the ANS.

Summary

NeuroScience's urinary neurotransmitter testing may reveal excesses and depletions that could be driving patient symptoms, but more importantly, are indicators of a patient's ANS function. By pairing this testing with advanced neurocircuitry knowledge, NeuroScience has developed next-generation solutions to influence central control of ANS function. Specifically, L-tyrosine ethyl ester is a key amino acid aimed at supporting central norepinephrine levels, and can be complemented by rationally selected additional ingredients such as L-glutamic acid, diosmin, and L-arginine. Centrally-acting formulations are likely to resolve multiple symptoms simultaneously and comorbidities and reduce the need for multiple interventions resulting in reduced patient cost and increased efficacy.

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