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Short Communication

Autonomic Dysregulation: An Unseen Epidemic

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Introduction

Occupied as we generally are on navigating our day-to-day demands, the essential mechanism we depend on to carry us through our various interactions operates, for the most part, invisibly. The apparatus in question is, of course, our nervous system, without which we would remain essentially motionless, and unable to carry out even the most remedial forms of action on our own behalf.

To the extent that the lion's share of our available time is absorbed with executing the various functions associated with our survival, it is no exaggeration to acknowledge that the fundamental integrity of our nervous system is, in fact, existential, and vital to the quality of our wellbeing. That's where stress comes in. While the overall impact that stress presents is well established, the appreciation of the magnitude of stress related processes is, to a large degree, limited; and fails to account for many of the affects that the long-term presence of stress produce when it comes to symptom generation.

In fact, accounting for the functioning of the nervous system provides a basis for apprehending the scope and breadth of stress related health concerns, which can be viewed as the very expression of autonomic nervous system dysregulation. The autonomic nervous system manages vital operations like heart rate, blood pressure and respiratory functions. Stress is said to produce autonomic imbalance through metabolic dysregulation between the sympathetic and parasympathetic branches, often due to excessive hyperstimulation [1]. Dysregulating autonomic balance can be the result of exaggerated sympathetic activation, in many instances accompanied by decreased parasympathetic output [2].

In one of its more fundamental examples, autonomic dysregulation can be seen as the underlying mechanism responsible for the development of a peptic ulcer, when an elevated abundance of stomach acid becomes routinely produced in response to either perceived stress, or stress related occurrences.

Similarly, headache generation can be fairly easily accounted for as the direct byproduct of stress-induced muscle tension, a straight-ahead cause-and-effect relationship that doesn't require much in the way of additional inspection. Fair enough. However, even run-of-the-mill stress responses are said to release a cascading combination of hormone-based stress reactions commonly referred to as fight-or-flight [3]. Chief among these secretions is a category of stress hormone called glucocorticoids, often referred to as cortisol. Interestingly, chronic cortisol hyper secretion is associated with psychosocial stress, and contributes to classic stress related symptoms like elevated blood pressure and anxiety [4].

A Multifactorial Response

For that matter, psychosocial stress has been found to be independently associated with cardiovascular disease (CVD), in a manner that depends upon an individual's response to a given stressor, along with the degree and duration of the stress itself [5]. These sorts of variations in interactions between individuals, environmental factors and physiological/psychological reactivity have increased recognition that "stress" is not a singular response, but instead takes place across a spectrum of multiple factors and repeated exposures that influence habitual responding, reactivity and the interaction of health behaviors with stress [6].

As stress investigator Robert Sapolsky puts it:

"The sympathetic nervous system and glucocorticoids play a role in the response of virtually all stressors. But the speed and magnitude of the sympathetic and glucocorticoid branches can vary depending on the stressor, and not all of the other endocrine components of the stress-response are activated for all stressors. The orchestration and patterning of hormone release tend to vary at least somewhat from stressor to stressor, with there being a particular hormonal 'signature' for a particular stressor" [7].

In attempting to account for the relative value that the differential patterning of autonomic responses provides, various researchers have calculated that when the *concurrent* activation of the glucocorticoid response to stressors, along with the sympathoadrenal branch is excessive or *prolonged*, the resulting 'distress' is responsible for producing a variety of clinical disorders [8].

Cumulative stress based on *chronic* fight-or-flight activation plays a principle role in nervous system dysregulation [9]. In some instances, cumulative stress has been found to be associated with poor mental health, maladaptive coping strategies and anxiety [10]. The varying outcomes contained within individualized response patterning and stress history underscore the increased recognition that rather than operating as a uniform response, stress is composed of a multitude of separate, interrelated reactions, each with it's own corresponding neurochemical signature.

As a result, it is not difficult to imagine instances when chronic or long-term stress impacts immune system functioning itself [11]. And while sympathetic nervous system overdrive is a recognized hallmark of cardiovascular disease and hypertension [12], autonomic dysregulation is also understood to influence the brain-gut interactions and mucosal inflammation underlying irritable bowel syndrome (IBS) [13]. Moreover, inflammation modulation in inflammatory bowel disease (IBD) is thought to be mediated by sympathetic nervous system imbalance in both Crohn's disease and ulcerative colitis [14].

Insofar as kidney functioning is concerned, chronic sympathetic hyperstimulation is implicated in renal disease progression and failure [15]. What's more, the metabolic effects that central sympathetic overactivity is said to produce include insulin resistance potentiation, augmented risk for type 2 diabetes and impaired baroreflex sensitivity [16].

Cellular and Molecular Influences

Considering the relationship between baroreceptor functioning and sympathetic arousal, it's not exactly a surprise that autonomic dysregulation could be involved in the pathogenesis of atrial fibrillation [17]. In fact, if one drills down to the molecular level, one way to view the contractile dysfunction characteristic of atrial fibrillation is as a means of attempting to protect muscle cells from cellular stress produced by potentially lethal calcium overloading [18].

The presence of calcium handling dysfunction as a byproduct of a stress-related response is a classic example of individual response patterning encompassing far more in the way of intricacy than standard fight-or-flight models might lead one to imagine [19]. A more comprehensive assessment of the potential influences stress encompasses might in fact include ion channel transport dysregulation, alterations in action potential properties and cellular electrophysiological variations [20].

Ion channels are membrane proteins that regulate the flux of ions into and out of cells [21]. Ion channel dysfunction helps explain the potassium ion perfusion and oxygen-glucose deprivation characteristic of the electrophysiological phenomenon known as spreading depolarization (SD), an event linked to various pathologies including traumatic brain injury (TBI), seizure, stroke and migraine. In these conditions, extreme changes in ion concentrations are associated with cellular swelling and modifications in glutamate [22].

Consistent with its role as the body's principle excitatory transmitter, changes in glutamatergic transmission due to evoked stress responses hardly qualifies as a major revelation [23]. More revealing however might be the relationship between dysfunctional glutamatergic neurotransmission, stress-related mental illnesses and neuropsychiatric disorders [24]. As circumstances would have it, the excitatory effect glutamate has on nerve cells can even excite cells to their own death, a process referred to as excitotoxicity [25].

When excitotoxicity becomes chronic, it has been found to contribute to various neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis (ALS), and Huntington's disease [26]. Beyond the link between stress, excessive glutamate release and neurodegenerative disorders, glutamatergic neurotransmission abnormalities also play a role in various psychiatric conditions including major depression, bipolar disorder and schizophrenia [27].

Channelopathies

Although not explicitly designated as a stress response per se, excessive extracellular glutamate concentration can be seen as the byproduct of a channelopathy, an autonomic dysfunction associated with ion channel mutations that disrupts homeostatic functioning [28]. While most frequently presented as being genetically determined, channelopathies are also described as being acquired [29], a distinction that might account for the effect that autonomic dysregulation has in conditions involving molecular pathophysiology [30].

To the extent that ion channel functioning constitutes a vital mechanism underlying synaptic transmission, it's not difficult to imagine various skeletal muscle disorders incorporating a

channelopathy involving muscle membrane hyperexcitability [31]. This condition, referred to as *myotonia*, involves sustained electrical activity at rest and spontaneous, repetitive firing of action potentials following activity [32], which by itself could easily account for increased levels of extrasynaptic glutamate.

As it turns out, excessive glutamate release leading to cellular damage as a result of excitotoxicity is recognized as being modulated by stress [33]. This would tend to include the impact that high levels of extracellular glutamate provide in conditions such as Parkinson's disease [34], schizophrenia, Alzheimer's and brain tumors [35]. When elevated extracellular glutamate concentration is uncontrolled, it can result in the continuous depolarization of neurons characteristic of conditions such as amnesia, anxiety, hyperalgesia and psychosis [36].

When viewed in its entirety, the scope of glutamatergic dysregulation constitutes an unseen epidemic [37], one that can broadly be accounted for as a byproduct of autonomic dysregulation, specifically encompassing central sympathetic overactivation [38]. When one accounts for the cellular, molecular and immune system influences that are contained within standard stress calculations [39], the resulting neurosignature expands the very definition of the stress response itself.

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Conflict of interest

No conflict of interest.

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