Stress Axis Dysfunction: A Common Finding in Schizophrenia and the Metabolic Syndrome?

Natasha Afzal · Jogin Thakore

Neuroscience Centre, St. Vincent’s Hospital Fairview, Dublin, Ireland

Abstract

Stress might be the unifying feature in both schizophrenia and the metabolic syndrome. It is possible that the perception of stress by those with schizophrenia is sufficiently altered so as to lead to a more frequent activation of the primary stress response, namely activation of the hypothalamic-pituitary-adrenal axis resulting in hypercortisolaemia. If so, this might lead to changes both in central (e.g. hippocampal function and structure) and peripheral effects (e.g. the adoption of a physical habitus characterized by upper body fat, insulin resistance/type 2 diabetes and ischaemic heart disease). Finally, ‘switching off’ of this stress axis may lead to reduction in both psychotic symptoms and metabolic derangements.

The metabolic syndrome (MetS) and illnesses that arise as a result of its presence are an integral part of schizophrenia. A debate still rages as to whether they are a consequence of certain neuroleptics that are commonly used in its treatment. Despite a huge increase in papers on the topic there is as such no definitive answer. What is clear is that many of these problems may be present before the onset of the illness (for example, in high-risk individuals) or before the commencement of treatment. An alternative explanation for the co-existence of schizophrenia and the physical states mentioned may be that they arise in parallel from a ‘common soil’. A mediating factor for both may be dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis.

This chapter aims to put forward evidence for this hypothesis. It will show how there is overactivity of the HPA axis in both schizophrenia and the MetS. The start of the chapter briefly outlines the normal function of the stress axis after which there is a description of how this endocrine system malfunctions in schizophrenia, both centrally and peripherally. Commonality between the physical manifestations of schizophrenia and Cushing’s syndrome are enumerated. Finally, there is discussion about
how stress may lead to the MetS and how pharmacological treatments for schizophrenia and MetS may work by effecting the HPA axis.

Hypothalamic-Pituitary-Adrenal Axis: Normal Physiology

From a physiological perspective, the response to stress is mediated by the HPA axis. A full description of this regulatory process is beyond the scope of this chapter and the reader is referred to Charmandari et al. [1] and Tsigos et al. [2] for a more comprehensive review. One of the primary mammalian responses to stress, be it psychological or physical, is activation of the HPA axis. In essence, the stressor stimulates the production and release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. CRH in turn causes the production and secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. CRH is the prime secretagogue of ACTH though in situations of chronic stress this role is probably deferred to arginine vasopressin (AVP). ACTH travels to the adrenal glands where it stimulates the production and release of glucocorticoids (GC) such as cortisol. This series of hormonal releases occurs as a cascade and is termed the feedforward limb. As the HPA axis is a closed-loop system, cortisol acts to regulate its own secretion (feedback activity) by acting at a number of sites both peripherally (pituitary) and centrally (hypothalamus and hippocampus). Cortisol acts on mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) to maintain the circadian variation of the HPA axis. MRs are high-affinity receptors which are predominantly occupied under basal conditions and help maintain HPA axis tone, while GC, low-affinity receptors, are bound during times of stress and play a major role in ‘switching off’ the HPA axis. The hippocampus by virtue of the fact that it contains both MR and GR (the latter are also found in other areas of the CNS) plays a critical role in regulating HPA axis activity.

Hypothalamic-Pituitary-Adrenal Axis Dysfunction in Schizophrenia

A number of different groups measuring the HPA axis at rest have observed hypercortisolaemia and elevated ACTH levels in schizophrenia though this is not a universally reported finding [3–9]. There are probably a number of reasons why this is the case but the 3 most likely are differences in methodology, patients were receiving antipsychotic medication at the time of testing, or patients had been abruptly withdrawn from medications in order to produce a ‘medication-free’ scenario. Antipsychotics dampen activity of the HPA axis and such actions may occur via or independently of their actions on various monoaminergic systems [10]. Support that schizophrenia itself may be associated with increased HPA axis activity has come from endocrine and neuroimaging studies in drug-naïve first-episode patients (10% larger pituitary
volume) and high-risk subjects (who showed a 20% increase of developing psychosis with each further 10% increase in pituitary size) [11].

Dynamic challenges of the HPA axis have also provided conflicting results probably for the same reasons quoted above. That aside, the dexamethasone suppression test (dexamethasone normally inhibits the secretion of ACTH and cortisol) is abnormal in nearly 50% of subjects with schizophrenia [12] though this is not a very sensitive test as such findings have also been shown in post-traumatic stress disorder [13] and Alzheimer’s disease [14]. Delta-9-tetrahydro-cannbinol, an active cannabis ingredient, when given to subjects with schizophrenia results in high cortisol levels and can cause a heightening of positive, negative and cognitive symptoms [15]. ACTH increases are greater in patients than matched controls when metabolic stress is induced centrally by 2-deoxy-D-glucose (2-DG) [5] while some investigators have shown that CRH-stimulated ACTH and cortisol are normal; however, pretreatment with dexamethasone leads to increased cortisol secretion in patients with established schizophrenia [16].

Vasopressinergic function is altered in schizophrenia as is indicated by the higher than expected rates of syndrome of inappropriate antidiuretic hormone section [17, 18]. Furthermore, osmotic stimuli [19] resulted in patients secreting greater amounts of ACTH and cortisol despite secreting similar amounts of AVP, while Jansen and Gispen-de Wied [20] subjected patients to psychosocial and physical stressors but found that only the former resulted in a blunted cortisol response. Metoclopramide is unique in its ability to stimulate AVP release and does so without altering plasma intracellular glucose deprivation, osmolality, or peripheral haemodynamics [9, 21–24]. Walsh et al. [25] have shown that metoclopramide induced patients to secrete higher levels of ACTH and cortisol though AVP responses were similar in first-episode drug-naïve patients and their matched controls, a finding that may be explained by the fact that conditions of chronic stress increase pituitary responsiveness to AVP [26].

Altered stress responses in schizophrenia may have genetic underpinnings as is suggested by the findings that unaffected siblings of those with schizophrenia have exaggerated ACTH responses to stress [27], while Myin-Germeys et al. [28] have shown that those at high risk have increased behavioural sensitivity to daily life stressors. Brunelin et al. [29] have shown that 2-deoxyglucose induces a greater release of ACTH and homovanillic acid (a breakdown metabolite of dopamine and noradrenaline) in patients with schizophrenia with siblings have a response intermediate to probands and controls.

Lack of or poorly functioning GR can also lead to an overactive HPA axis and such changes have been seen in subjects with schizophrenia. i.e. GR mRNA numbers in the frontal cortices, amygdala and hippocampus (dentate gyrus, CA1, CA3 and CA4) [30, 31] although these changes also occur in other psychiatric illnesses such as bipolar disorder and major depression [32]. Further evidence of GR dysfunction may come from the observation that acutely administered