

Stress and the genesis of diabetes mellitus in schizophrenia

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Background The incidence of diabetes mellitus is higher in patients with schizophrenia than in the general population. Antipsychotic drugs have been implicated in the development of diabetes, but as non-medicated patients with schizophrenia have high rates of diabetes it is likely that factors other than medication are involved.

Aim To examine the role of stress in the emergence of diabetes mellitus in patients with schizophrenia.

Method Selective literature review.

Results A model is developed suggesting that patients with schizophrenia show overactivation of both the hypothalamic–pituitary–adrenal and sympathoadrenal medullary axes, manifested by increased production of cortisol and adrenaline. Both of these hormones are known to be diabetogenic and are proposed as playing a part in the onset of diabetes mellitus in schizophrenia.

Conclusions Stress has an important role in the onset of schizophrenia and may also play a part in relapse. Further research is needed to clarify the extent to which stress accounts for the genesis of diabetes in such patients.

Declaration of interest T.G.D. has lectured at meetings and served on advisory boards organised by companies promoting antipsychotic medications, including Eli Lilly, Janssen-Cilag, Pfizer and AstraZeneca.

People with schizophrenia are exposed to a broad range of psychological stressors, which for the purpose of this paper are categorised as ‘true stressors’ or ‘pseudostressors’: true stressors emanate from objective space and are qualitatively similar to the stresses experienced by the population at large; pseudostressors emanate from subjective space and are only experienced by people with schizophrenia and other psychotic illnesses. Routine stresses of everyday life such as financial difficulties and problems in the work environment are objective stressors; although this type of stress is experienced by everyone, it can be significantly greater in people with schizophrenia, who are often at major social disadvantage. A form of objective stressor to which people with schizophrenia seem especially vulnerable has been termed expressed emotion (EE). This form of stress originates in the home environment, and includes critical commentary and emotional overinvolvement (Brown *et al.*, 1972). It has been demonstrated consistently that patients with schizophrenia are especially prone to relapse in high-EE environments. Optimising therapy involves appropriate pharmacological intervention together with education and other approaches to reduce the level of expressed emotion in the home environment.

Pseudostressors, originating in subjective space, are represented by the core symptoms of schizophrenia, namely delusions and hallucinations. These stressors can have profound emotional intensity, which can render them both qualitatively and quantitatively different from the stresses experienced by the rest of the population. The biological impact of such stressors has been only superficially explored, but given the behavioural disturbance they can produce, it is reasonable to assume that they also lead to major endocrinological changes.

METHOD

A selective review was made of papers on Medline. Secondary sources such as book chapters were also searched.

RESULTS

Stress endocrinology

The endocrine stress system has two broad components with considerable central anatomic interconnection. The acute response to stress, which usually lasts a few minutes, consists of sympathetic adrenal-medullary (SAM) activation. The chronic stress response is mediated by the hypothalamic–pituitary–adrenal (HPA) axis. Cannon (1932) proposed the concept of homeostasis, whereby bodily systems are regulated to maintain a steady state. Such a view has significantly influenced the development of modern integrative physiology. The SAM axis has a fundamental role in homeostasis and is regulated at a pontine level by the locus coeruleus, a noradrenergic nucleus which provides a highly arborised neuronal network influencing levels of arousal and vigilance. The SAM system controls acute reaction to stress in what Cannon described as the ‘fight or flight’ response. He demonstrated that without a sympathetic nervous system an animal could survive in an unstressed environment; however, when subjected to stress, the animal could not mount basic physiological responses such as mobilisation of glucose. Activation of the SAM axis results in secretion of the catecholamines adrenaline and noradrenaline from the adrenal medulla, which is essentially an enlarged and highly specialised sympathetic ganglion. Because these catecholamines regulate acute responses they have short half-lives (1–3 min), with a high metabolic clearance rate and rapid degradation by catechol O-methyltransferase, monoamine oxidase and aldehyde oxidase (Esler *et al.*, 1990).

Adrenaline and noradrenaline exert their impact through α - and β -adrenoceptors (Ahlquist, 1974). Adrenaline is most potent at β_1 - and β_2 -receptors, with far less effect on α -receptors, whereas noradrenaline is more potent at α -receptors. The hyperglycaemic impact of the adrenomedullary hormone is mediated by adrenaline, which is a profoundly diabetogenic hormone. Adrenaline produces a hyperglycaemic effect in that it both stimulates hepatic glucose

production and also limits glucose utilisation. The hepatic effect is mediated largely through β -adrenergic stimulation, although α -adrenergic stimulation may have a part to play (Macdonald, 1999). The impact of adrenaline on glucose production is transient and takes place within minutes. The ability to limit glucose utilisation occurs predominantly through the β -receptor. As a result of this impact on glucose utilisation, sustained hyperadrenalism produces sustained hyperglycaemia.

Noradrenaline exerts hyperglycaemic actions when released from axon terminals of sympathetic post-ganglionic neurons. The liver has an important sympathetic innervation, and in animals when these sympathetic nerves are electrically stimulated a decrease in glycogen content is reported, together with increased hepatic glucose release, resulting in hyperglycaemia (Lautt, 1980). There is no evidence that this system is involved in the regulation of carbohydrate metabolism under normal circumstances, but it comes into play in situations of significant stress. Interestingly, Kjaer *et al* (1995) reported that the liver denervation that occurs with transplantation does not cause a gross alteration in carbohydrate metabolism. The primary metabolic impact of the SAM axis is control of fat metabolism (Nijima, 1989). Prolonged starvation and other significant stressors increase lipolysis through the SAM response mediated by β -adrenoceptors. In marked contrast, stimulation of α -adrenoceptors inhibits lipolysis in adipose tissue. Although the sympathetic innervation of white adipose tissue mainly supplies the vasculature, in some areas there is direct innervation of the adipose cells. Overall, brown adipose tissue has a greater vascular supply and innervation than white tissue and a greater percentage of these cells are sympathetically innervated, with the metabolic effects again mediated through β -adrenoceptors. Stimulation of the sympathetic innervation of the pancreatic β -cells produces an inhibition of insulin release mediated by α -adrenoceptors, probably of the α_2 subtype. When the SAM system remains activated there is a reduction in the effectiveness of insulin to stimulate glucose uptake and utilisation. Such an impact is produced through the β_2 -adrenoceptors and is mimicked by drugs such as salbutamol and terbutaline. High doses of β_2 agonists stimulate adipose tissue lipolysis and induce pancreatic glucagon secretion,

which can lead to increased ketone production.

Function of the SAM axis in schizophrenia

No comprehensive study has used contemporary assays to examine SAM function in schizophrenia. Kemali *et al* (1985) examined catecholamine release over 24 h in patients with schizophrenia and a matched comparison group; the patients had been drug-free for a minimum of 2 weeks. Plasma noradrenaline levels were consistently elevated in the patients during the waking period but not during sleep. In a similar study, Barbeito *et al* (1984) found an elevation in catecholamine levels in both plasma and urine, and their data support the view that urinary catecholamine measurement could be used as a reliable assessment of SAM activity in schizophrenia. The finding is consistent with a report that unmedicated patients with schizophrenia have elevated levels of noradrenaline as well as heightened responsiveness on measures of electromyographic activity, skin conductance and heart rate (Albus *et al*, 1982); the patients showed an attenuated response to the cold pressor test, noise and mental arithmetic stressors. A more recent study by Fleischhaker *et al* (1998) reported that response to clozapine in patients with treatment-resistant schizophrenia was associated with increases in adrenaline levels, a finding that might help to explain the pro-diabetic effect of this drug.

Hypothalamic–pituitary–adrenal axis

The ability to sustain a stress response is dependent on chronic activation of the HPA axis. Its major hormones are well defined and are easily assayed. The pro-hormone pro-opiomelanocortin is produced in the corticotrophs of the anterior pituitary and has a pivotal role in the axis. Its cleavage results in the production of adrenocorticotrophic hormone (ACTH), β -endorphin and several other biologically active peptides. The release from the adrenal cortex of cortisol, dehydroepiandrosterone (DHEA) and other steroids is stimulated by ACTH. Corticotrophin-releasing hormone (CRH) and arginine vasopressin are the major secretagogues of the HPA stress system. Corticotrophin-releasing hormone, a 41 amino acid peptide originally discovered and sequenced by Vale *et al* (1981), is produced in the medial parvocellular neurons of the paraventricular

nucleus of the hypothalamus. These neurons project to the external zone of the median eminence, where CRH is released into the portal vasculature to act on CRH type 1 receptors of the anterior pituitary. The hormone acts synergistically with arginine vasopressin in bringing about ACTH release from the corticotrophs. Following its identification in 1954, vasopressin, a nonapeptide, was considered to be the principal factor in the regulation of ACTH release, but with the subsequent elucidation of the structure of CRH and the domination of the 'one neuron – one transmitter' principle, the role of CRH came to supersede that of arginine vasopressin. It is now apparent that in stress-free situations CRH is the dominant regulator of the HPA axis, but with chronic stress many paraventricular neurons that normally produce CRH begin to co-express arginine vasopressin (Scott & Dinan, 2002). In these circumstances arginine vasopressin plays an important part in sustaining HPA activation. The CRH₁ receptor downregulates with increased production of CRH, while increased production of arginine vasopressin upregulates the V_{1b} receptor. This latter effect is important in maintaining high cortisol output in the presence of a chronic stressor. In the absence of such a mechanism, adrenocortical activity will decrease over time and prevent an adequate biological response to the chronic stress.

The HPA axis is well characterised and has been investigated in a variety of central and peripheral disorders. In depression, HPA dysregulation has been extensively investigated, but in schizophrenia HPA function has received far less attention.

Function of the HPA axis in schizophrenia

Given that the onset of schizophrenia is frequently precipitated by stress and that relapse often takes place in a similar setting, it is surprising that the investigation of stress at a biological level has received so little attention in schizophrenia research. Walder *et al* (2000) assayed cortisol levels in multiple salivary samples from people with schizophrenia. This technique has the advantage of being stress-free, and as the cortisol in saliva is unbound to protein, the assay provides a measure of biological activity. They found that cortisol levels were significantly elevated, and that the greater the severity of symptoms the greater the elevation. The results support the view

that the psychotic features of schizophrenia generate considerable biological stress. In a study of 53 patients taking medication, Kaneda *et al* (2002) found elevated levels of ACTH but failed to find abnormalities in plasma cortisol. Demonstrating differences in the latter usually requires multiple sampling, even in patients with overt Cushing's disease. The dexamethasone suppression test is a test of delayed feedback mechanisms in the HPA axis. In patients with predominantly positive symptoms a non-suppression rate of 56% was reported; patients with negative symptoms had a non-suppression rate of 53% (Pivac *et al*, 1997). These results are similar to those observed in major depression and are clearly different from those observed in healthy individuals. In a similar study Muck-Seler *et al* (1999) reported high baseline cortisol levels in schizophrenia with a non-suppression rate of 50%, and Plocka-Lewandowska *et al* (2001) reported data suggesting that patients with schizophrenia who are suicidal are most likely to be non-suppressors. These studies support the view that defective HPA feedback mechanisms, possibly due to insensitive glucocorticoid receptors, may have a causative role. Levels of CRH in the cerebrospinal fluid have been investigated by Banki *et al* (1987): in patients with schizophrenia they found levels that were above normal, but not as high as those observed in patients with melancholic depression. The dexamethasone-CRH test has been applied to patients with schizophrenia (Heuser *et al*, 1994). This test involves the administration of dexamethasone at 23.00 h and the administration of CRH on the following day at 15.00 h. Paradoxically, the dexamethasone pretreatment enhances the response to CRH in healthy individuals, and this enhancement is augmented in patients with major depression. Heuser *et al* (1994) found that patients with schizophrenia release more cortisol and ACTH after the dexamethasone-CRH test than do age-matched healthy controls.

Few investigators have employed non-pharmacological strategies to activate the HPA axis in schizophrenia. Jansen *et al* (2000) used public speaking as a psychological stressor in patients with schizophrenia, and measured their salivary cortisol response to this stress. The patients showed a blunted response, in contrast to their response to the physical stress of cycling.

CLINICAL IMPLICATIONS

- Psychotic stress can produce a transient suppression of pancreatic β -cell function and alter insulin sensitivity.
- Cortisol has a pronounced antagonistic impact on insulin-mediated inhibition of hepatic glucose release while simultaneously decreasing glucose utilisation in muscle and reducing the binding affinity of insulin receptors.
- Increase in the production of the diabetogenic hormones cortisol and adrenaline may help explain the increased tendency of patients with schizophrenia to develop diabetes.

LIMITATIONS

- Many of the studies reported are characterised by small sample size.
- Studies of adrenaline production in schizophrenia are dated and made use of assays with low sensitivity and specificity by present standards.
- No large-scale prospective study examining stress hormones and glucose in schizophrenia has been published.

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Stress and glucose regulation

There has been no systematic research to date exploring the endocrine response in people with schizophrenia exposed to a high-EE environment. This is surprising given the large number of studies published, especially in the UK, on high expressed emotion and schizophrenia. However, Shiloah *et al* (2003) examined β -cell function and insulin sensitivity using the homeostasis model in non-diabetic patients with schizophrenia who had acute psychosis. A total of 39 individuals were assessed and the homeostasis model assessment was based on two samples of glucose and insulin. Stress was assessed using the Clinical Global Impression (CGI) scale, which rates psychological stress as a score of 0–7 (Guy, 1976). On admission the mean CGI score of the patients was 5.3 (s.d.=0.8) and on discharge it was 1.6 (s.d.=0.7). Patients with the highest CGI scores on admission had the highest glucose and insulin levels. Mean β -cell function was lowest on admission (96.8%, s.d.=33.2%) and highest at discharge (134.4%, s.d.=60.0%). In marked contrast, mean insulin sensitivity was

highest on admission (101.7%, s.d.=36%) and had decreased significantly by discharge (77.1%, s.d.=34.8%). However, insulin sensitivity inversely correlated with CGI score: a high CGI score was associated with low insulin sensitivity, and a low score was associated with high insulin sensitivity. The data support the view that psychotic stress produces a transient suppression of β -cell function and alters insulin sensitivity.

The impact of psychosis on glucose tolerance in drug-naïve patients with first-episode schizophrenia has been reported by Ryan *et al* (2003), who compared 26 patients with schizophrenia and a similar number of control participants matched for age and gender. Four of the patients and none of the comparison group had an impaired fasting blood glucose concentration as defined by the American Diabetes Association (1997): >6.1 mmol/l (>110 mg/dl) and <7.0 mmol/l (<126 mg/dl). Patients had higher mean fasting levels of glucose and insulin. Furthermore, they had elevated cortisol levels, raising the possibility that the dysregulation in glucose homeostasis is secondary to overactivation of the HPA.

Effect of glucocorticoids

Glucocorticoids inhibit insulin function in a variety of ways. Cortisol has a pronounced antagonistic impact on insulin-mediated inhibition of hepatic glucose release while simultaneously decreasing glucose utilisation in muscle and reducing the binding affinity of insulin receptors (Meyer & Badenhop, 2003). When patients are treated with glucocorticoids over long periods almost half of them develop deranged glucose metabolism, and in half of these patients this dysregulation persists even after reduction or withdrawal of the glucocorticoid. This situation is analogous to that occurring in schizophrenia, where glucose homeostasis may be altered during acute episodes of illness and where the overall emergence of type 2 diabetes mellitus is higher than that seen in the general population.

DISCUSSION

A stress model of schizophrenia can help explain the tendency of people with this disorder to develop disturbance in glucose homeostasis. Numerous studies report overactivation of the HPA axis with attenuated feedback inhibition and increased cortisol output. Although the SAM axis has been less extensively studied, the available evidence suggests that people with schizophrenia have heightened SAM responses with increased adrenaline output. Intermittent or sustained increase in the activity of these core endocrine stress systems with increase in the production of the diabetogenic hormones cortisol and adrenaline may help to explain the increased tendency of such patients to develop diabetes. Such a biological vulnerability would render individuals even more susceptible to the negative effects of poor diet and lack of exercise.

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