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THE STRESS-VULNERABILITY MODEL HOW DOES STRESS IMPACT ON MENTAL ILLNESS AT THE LEVEL OF THE BRAIN AND WHAT ARE THE CONSEQUENCES?

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SUMMARY

Introduction: *The stress -vulnerability model (Zubin et al. 1977) is an extremely useful model for identifying and treating relapses of mental illness. We accept that human persons carry genetic and other predisposition to mental illness. However, the question arises as to how stress impacts on a person in order to cause mental illness to develop. Furthermore there arises the issue as to what other effects such stress has on the human body beyond the human brain.*

Our aim was to research and integrate the current literature in order to establish how stress impacts on the brain at the cellular level, and to establish whether there are other consequences for the human body brought about by the impact of stress on the human brain.

Method: *Literature Search, using pubmed.*

Results: *We have identified much literature on how stress affects biological mechanisms within the brain, and how it relates to biological vulnerabilities carried by different individuals.*

Conclusion: *We have identified communalities in how the interplay between stress and vulnerability occurs in different disease processes.*

Key words: *stress – vulnerability - hypothalamo-pituitary axis – epigenetics – depression - bipolar disorder - schizophrenia*

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INTRODUCTION

The stress -vulnerability model (Zubin et al. 1977) is an extremely useful model for identifying and treating relapses of mental illness. We accept that human persons carry genetic and other predisposition to mental illness. However, the question arises as to how stress impacts on a person in order to cause mental illness to develop. Furthermore there arises the issue as to what other effects such stress has on the human body beyond the human brain.

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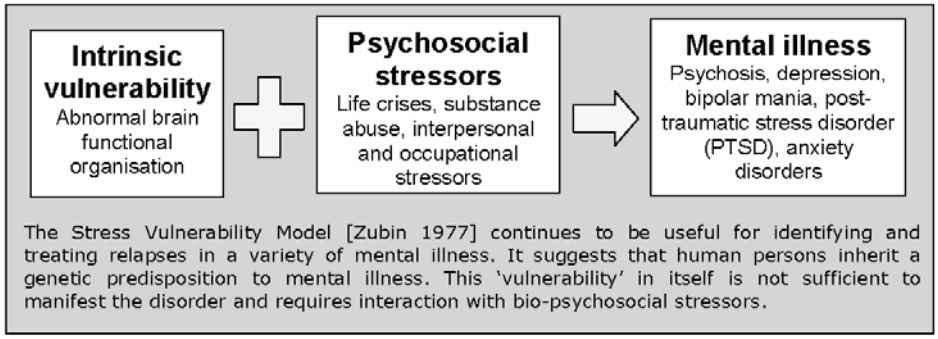

Figure 1. The stress-vulnerability model

METHOD

A Literature Search was carried out, using the pubmed database.

RESULTS

The link between the hypothalamo-pituitary-adrenal (HPA) axis and the development of mental illnesses like depression (Nestler et al. 2002), psychosis (Pariante et al. 2004, Garner et al. 2005), bipolar mania and anxiety disorders is well documented in the literature.

In response to stress,hypothalamic neurons containing corticotropin-releasing factor (CRF) increase synthesis and release of corticotropin (ACTH), b-endorphin, and other pro-opiomelanocortin products from the anterior pituitary gland.

Some of the hypothalamic neurons which regulate stress belong to that system which has orexin as its neurotransmitter; they increase arousal, locomotor activity, and cardiovascular response, and also link with other orexin neurons in the hypothalamus which regulate the reward mechanism, thus linking the two systems (Xiu et al. 2009).

Chronic stress results in persistently elevated levels of cortisol. In all the above conditions, stress has been showed to lead to an imbalance in pro- and anti-inflammatory cytokines in brain, with increased pro-inflammatory cytokines mediating enhanced production of corticotrophin-releasing factor (CRF) in the hypothalamus. The resultant persistent hypercortisolaemia induces glucocorticoid receptor tolerance thus impairing the negative feedback mechanism of the HPA axis. This also results in neurodegenerative changes in the hippocampus (Myint 2009), which is involved in mood regulation together with the prefrontal cortex and the amygdala. The hippocampus is rich in corticosteroid receptors (Reul et al. 1986) and contributes to regulatory inhibitory feedback of the HPA axis (Squire et al. 2000, Fanselow 2000). Hippocampal dysfunction may be responsible for inappropriate context dependent emotional responses (Davidson et al. 2002). Hence, a cytokine-mediated immunological response may provide the link between hypercortisolaemia and hippocampal damage in chronic stress.

Neuroimaging using MRI demonstrates that there is loss of hippocampal volume in many mental illnesses, reflecting the hippocampal atrophy described above. This occurs in Schizophrenia (Sumich et al. 2002), Post-traumatic Stress disorder (Felmingham et al. 2009), Borderline personality disorder (Weniger et al. 2009), and Depression (Sheline et al. 1999). In Bipolar disorder, there are reports that the hippocampus is actually enlarged (Javadapour et al. 2010, Jaracz 2008), however, reduction in concentration of hippocampal N-acetylaspartate, a marker of neuronal loss, has been demonstrated in patients with bipolar disorder (Deicken et al. 2003).

In Depression (Jaracz 2008), Post-traumatic Stress Disorder (Rogers et al. 2009), and Borderline personality Disorder (Weniger et al. 2009), the Amygdala are reduced in size. This causes no surprise since the amygdale are associated with fearfulness (van der Plas et al. 2010). However, in Bipolar Affective disorder, the amygdale are reported to be enlarged (Almeida et al. 2009).

At the level of the pituitary, a number of observations of changes in pituitary volume have been noted in various conditions; Thus in Schizophrenia, the pituitary enlarges during the prodromal stage of psychosis, and then shrinks after the first episode (Garner et al. 2005, Pariante et al. 2004).

Major depressive disorder (MDD) has been associated with increased pituitary gland volume, but a recent study found no significant Pituitary Gland Volume between patients currently suffering from depression, patients whose depression had remitted and healthy controls, thus Pituitary Gland Volume is not a useful marker of current or past MDD in adult patients (Lorenzetti et al. 2009). In Bipolar I Affective Disorder, patients have been recently shown to have a significantly larger pituitary volume as compared with controls, but there was no association between pituitary volume and illness duration, number of manic/ depressive episodes, daily medication dosage, family history, or clinical subtype (i.e., psychotic and non-psychotic). (Takahashi et al. 2009a, Takahashi et al. 2009b). Patients with Borderline Personality Disorder who suffered childhood trauma had smaller pituitaries than those who did not (Garner et al. 2007). The number of parasuicidal behaviours in patients with borderline personality disorder is also related to pituitary volume (Jovev et al. 2008).

Hence Neuroimaging using MRI is a very useful way of demonstrating both the stress related changes in the Hippocampus and those in the pituitary in numerous psychiatric conditions.

At the intracellular level, it has also been established that cortisol impacts on the balance between trophic and atrophic factors within neurons, thus affecting neurogenesis and brain plasticity in areas like the hippocampus and the frontal cortex. Neurogenesis is particularly stimulated by the trophic factors BDNF and BCL-2 (Gould et al. 2000). Reduction in the levels of such trophic factors in depression may account for reduced hippocampal size observed on MRI (Sheline et al. 1999). Hippocampal volume is also reduced in schizophrenic illness (Sumich et al. 2002).

It is known that the concentration of neuro-transmitters like serotonin in the synaptic cleft is modulated by drugs, such as the SSRIs, and by the serotonin transporter (SERT) (Richelson 2003). Polymorphisms in the SERT gene have been shown to influence different individual responses to stress (Lesch et al. 1996), an example of a direct stress-vulnerability interaction. Serotonin release into the synaptic cleft activates receptors that trigger BDNF gene transcription, leading to increased production of BDNF, which has a protective role in the development of brain neurons. Under stressful conditions, however, the BDNF gene is not activated, and lack of BDNF in the hippocampus may result in neuron atrophy or death (Stahl 2000).

Other monoamine neurotransmitters may well be involved in similar mechanisms to affect down-stream BDNF production (Duman et al. 1997). It is worth noting that there is accumulating evidence that atypical antipsychotics also seem to stimulate neurogenesis (Wakade et al. 2002), and that the concentration of BDNF appears important in the development of psychosis (Ho et al. 2007). Therefore, it appears that stress influences development of psychotic illness by mechanisms that are common to many different mental illnesses.

Through a system of polygenic inheritance, the interplay of many genes, each of small effect, influences

how an inherited genetic or other vulnerability for mental illness ultimately develops into a specific mental illness with unique manifestations in each individual (Craddock et al. 2005a, Craddock et al. 2005b).

Furthermore, it has been now shown that Epigenetic factors modify the brain's response to stress. This has been demonstrated by differences in a neuron-specific glucocorticoid receptor promoter (NR3C1) in postmortem hippocampi of suicide victims who have suffered child abuse and controls. Thus abuse alters the HPA function and increases suicide risk (McGowan et al. 2009). Indeed parental care may affect regulation of hippocampal glucocorticoid receptor expression.

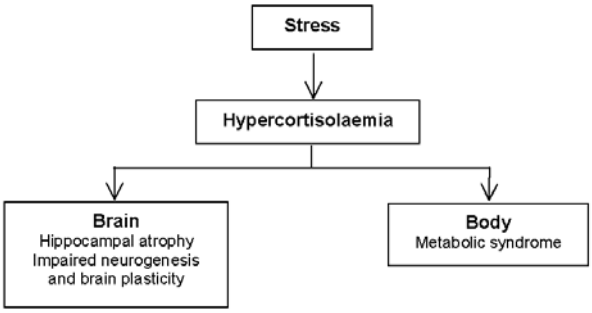

Figure 2. The effects of stress on the brain and the body

However, the effects of heightened cortisol levels are not confined to the brain. Global metabolic effects of hypercortisolaemia are those of the 'Metabolic Syndrome' (Musselman et al. 1998). There is much evidence in the literature that diabetes is more likely to develop in schizophrenia than the ordinary population, even before commencing anti-psychotic medication. Recently, there has been clear evidence from PTSD in the Bosnian War that metabolic changes such as raised cholesterol levels occur in patients with this illness (Dzubur Kulenović et al. 2008). In psychosis, it is certain that stress is an important factor in the development of the illness (Pariante et al. 2004, Garner et al. 2005), but cardiovascular risk factors are under-diagnosed in these patients (Bernardo et al. 2009). It appears that whilst genetic factors may influence the onset of diabetes in psychotic patients (Herken et al. 2009), obesity and possibly hyperlipidaemia is linked with the use of anti-psychotic medication (Verma et al. 2009). Therefore, the development of metabolic syndrome in psychosis must be viewed as multi-factorial.

DISCUSSION

Finally, we may now look at similarities and differences in how patients with different conditions respond to stress; the similarities argue for a common pathway by which stress affects patients with different vulnerabilities who suffer from mental illnesses. The differences are pointers towards different vulnerabilities, and hence different conditions or mental illnesses.

Similarities between how different conditions respond to Stress (Schizophrenia, Bipolar Disorder, PTSD, Depression)

- Stress is mediated in all illnesses by the HPA Axis.
- The Common effect of stress in all illnesses is therefore Hypercortisolaemia.
- The Effect of Hypercortisolaemia is to affect the balance between trophic and atrophic factors in neurons.
- There are many similarities in neuroimaging (MRI) changes in These illnesses in the Hippocampus, Amygdala, and Pituitary volume.
- Neurotransmitters, via second messengers (Cyclic AMP, CREB) modulate concentration of BDNF intracellularly.
- BDNF (and BCL-2) is a common trophic factor in all conditions.
- The Immune (cytokine) response to Hypercortisolaemia is the same for all conditions in Hypothalamus.
- Glucocorticoid receptors in the Hypothalamus respond to stress similarly in all conditions.
- Hypercortisolaemia causes peripheral effects- on cholesterol and glucose metabolism and on atherosclerosis and hypertention in all conditions.

The above constitutes a common mechanism whereby stress may provoke illness in patients with a specific constitutional vulnerability.

Differences between how different conditions respond to Stress (Schizophrenia, Bipolar Disorder, PTSD, Depression)

- Different illnesses relate to different neurotransmitter systems e.g. dopamine in schizophrenia, serotonin and noradrenalin in depression. These via second messengers modulate concentration of BDNF intracellularly.
- Hence different illnesses relate to specific genes; e.g. SERT in Depression, multiple genes in schizophrenia and bipolar disorder, various genes in PTSD, etc.
- Some specific trophic factors are more related to specific conditions e.g. BAG-1 to bipolar disorder.
- In at least one illness- bipolar disorder, there are differences between the Neuroimaging changes in the Hippocampus, amygdale, and pituitary volume from the other conditions.
- As a result of the interplay between genes for Diabetes and Schizophrenia, there is an increased risk of diabetes and schizophrenia, and also specifically increased vulnerability to diabetes with certain treatments (beyond adiposity) to certain treatments (e.g. clozapine and olanzapine).

The above constitute a constitutional genetic vulnerability to particular illnesses.

Hence we can argue that there is a biological model which explains both the 'Stress' and the 'Vulnerability' models of the Zubin and Spring 'Stress/Vulnerability Model' for development of mental illness in not only schizophrenia, but a number of important mental health conditions, and that this response to stress is similar and equally deleterious in all these conditions, though individual genetic vulnerabilities may make these responses more serious in different illnesses.

CONCLUSION

It appears that stress influences the development of many mental illnesses by common mechanisms. The effects of stress need to be seen as being a process of linked consequences, beginning with increased cortisol levels affecting areas of the brain like the hippocampus and the HPA axis, leading to alterations in intracellular levels of trophic factors such as BDNF in neurons, ultimately affecting neurogenesis and plasticity of the brain. Stress also results in metabolic changes which include many of the cardiovascular risk factors that contribute to the Metabolic Syndrome. These changes were formerly solely attributed to the effects of medications that alleviate mental health symptoms by reversing the atrophic effects of stress. Hence, in assessing mental illness and planning its treatment, it is necessary to separate the deleterious effects of stress itself from the effects of medication.

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