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REVIEW ARTICLE

DEPRESSION: FEW LESSER KNOWN CAUSES

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ABSTRACT

Cognitive deficits and elevated cortisol level are considered as the hallmark of depression. Actual causative factor for cognitive changes and depression are not well understood. Various studies summarize one or other factors like cortisol in causation of cognitive changes and depression. However complete model based study is required signifying all the causative factors. Hippocampus in brain is closely related to cognitive functions. As mineralocorticoid and glucocorticoid receptors are present majorly in hippocampus through which cortisol exerts its action. So the association of cortisol with depression and cognitive changes is emphasized more till date. In time, depression and cognitive changes development has changed from age related to stress related and later to more complex mechanisms like immune reaction. Stressful life event in various studies had been correlated with increased cortisol level which they considered as the main biological factor. But other factors like immune reaction, IDO pathway, 5-HT precursor tryptophan may equally contribute in development of these changes. Sum up of all factors in an individual is more important in development of cognitive deficits and depression. So a newer approach should be designed considering other factors summarized in this review to develop a model based approach.

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INTRODUCTION

Depression and cognitive changes of different causes and etiologies has been associated with increased level of cortisol and decreased level of serotonin (5-Hydroxytryptamine, 5-HT). increased level of cortisol lowers the level of 5-HT and acts as causative factor for depression. This postulation has remained in controversies which was further footed strong in the studies done at department of psychiatry at Manchester University and found no evidence of increase in salivary cortisol levels in large women population having depression or vulnerable to depression with or without adverse social or personal circumstances (Cowen, 2002). In studies done by Bauer *et al* in 2000; and Da Roza Davis & Cowen in 2001 authors did not found elevated cortisol level in a subgroup of participants who had experienced a recent stressful life event whether or not they were currently depressed. In addition, there are growing evidences that some specific kind of chronic difficulties for example, caring for a relative with dementia, can be associated with elevated cortisol level. Therefore it appears that life events and stressful events may cause cortisol hypersecretion but this may not necessarily lead to development of depressive disorder (Bauer *et al.,* 2000; Da Roza Davis and Cowen, 2001). In an animal study done by Mc Allister-William *et al*, 2001 it was suggested that elevated cortisol level may actually enhance 5-HT neurotransmission by decreasing the sensitivity of inhibitory 5-HT_{1A} cell body autoreceptors. This study guided the role of other environmental and genetic factor along with hyperpersecretion of cortisol in development of depression. From the studies we may have to accept that increased secretion of cortisol alone is not an individual pathophysiological factor (Mc Allister-williams *et al.,* 2001).

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Depression and tryptophan: are they linked ?

In contrast to above, it was found that women with depression were having more 5-HT function of brain. This was judged by the prolactin response after administration of 5-HT releasing agent d-fenfluramine. Prolactin response was increased instead of getting decreased. These findings lead to study of other causes of depression and cognitive declines in both young as well as elderly population (Strikland *et al.,* 2002; Maes *et al.,* 1989). It was also found that in mild or moderate depression there was increase in 5-HT neurotransmission. The actual mechanism of which was not known but thought to be due to 5-HT_{2c} post-synaptic neurotransmission. These 5-HT_{2C} receptors are activated by the adverse conditions and causes anxiety

which is characteristic of this type of depression. The prolactin response to fenfluramine may be to indirect response to 5-HT_{2c}. The above said mechanism may not be true to all types of depression or cognitive impairments (Goodall *et al.,* 1993). Due to these inconsistencies in the above mentioned findings it compelled the investigators to search for other causative factors for cognitive deficits and depression. Strickland *et al* had a major breakthrough and suggested the role of tryptophan in depression. They found that in women with depression had low level of tryptophan: branched chain amino acids (BCAA) ratio. The synthesis of 5-HT in brain depends upon the availability of amino acid precursor tryptophan. Tryptophan competes with BCAA for transport across the blood brain barrier and therefore tryptophan to BCAA ratio was important in 5-HT synthesis in brain (Fenstorm and Wurtman, 1971).

In other studies too it is well documented with low levels of tryptophan in depression. Further, chronic decrease in tryptophan causes the increase in prolactin response to d-fenfluramine (Walsh *et al*., 1995). This up regulation was due to increased receptor sensitivity of 5-HT_{2C}. It helps in adaptive response mechanism to the decreased 5HT synthesis (Cowen *et al*., 1995) this mechanism of adaptive increase may be the cause of increased prolactin response (Cowen *et al.,* 1995) to fenfluramine. Strikland *et al* do not supported these findings and emphasized that decrease in plasma tryptophan was not alone the significant increased prolactin response to fenfluramine as there was no linear correlation between them (Strikland *et al*., 2002). Interestingly in few of the studies it was found that in women who were not depressed or cognitive deficits with a history of recent stressful event were having low level of tryptophan and their prolactin response to fenfluramine was normal. These findings suggested brain 5HT function is less sensitive to decrease in tryptophan. Therefore the subjects may be less sensitive to develop depression or cognitive changes. Investigating the cause of decreased tryptophan other than stressful life event requires further investigations. Depression and cognitive changes were also not seen in all patient of nutritional deficiency of tryptophan.

A viscous circle: cortisol, tryptophan and depression

The magnum of events above indicated that there may be some relation between cortisol level and tryptophan? This was emphasized further in few studies where the subject suffered stressful or severe life event with increased in cortisol value and low level of tryptophan. It was found that increased cortisol may induce 2,3-dioxygenase (tryptophan pyrrolase), the metabolizing enzyme of tryptophan. Increased cortisol level may decrease plasma tryptophan level in subjects with recent severe life events (Jensen *et al*., 2003). The same correlation was found in patients with dementia (Da Roza Davis and Cowen, 2001) by Da Roza Davis and Cowen, 2001. In other study done by Strickland *et al* found that women with depression or cognitive impairment demonstrated a decreased tryptophan:BCAA ratio despite having normal cortisol levels. So, it is important to find other causative factors for lowering of tryptophan level in subjects with severe life events other than focusing on cortisol alone. Other cause may be due to activation of immune system however the exact mechanism is still unknown (Van West and Maes, 1999).

Immune reaction a cause of cognitive changes & depression ?

In time course it has been proved that even the immune system plays a vital role in development of depression and cognitive changes. Depressed patients have been found to have higher levels of pro-inflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules, also therapeutic administration of Interferon-α (INF) for hepatitis C has been found to cause depression. INF is strongly associated with IDO activation. It was found that dysregulation of neurotransmistter serotonin (5-HT) is associated with sickness behavior and depression. In these patient both peripheral and central 5HT system was low, like low level of TRP, the precursor of 5-HT, central 5-HT transporter (5-HTT) function and changes in 5-HT_{1A} and 5-HT_{2A} brain receptors. So one way INF may induce depressive symptoms is by affecting the serotonergic systems (Marieke and Maes, 2004). The exact mechanism for cognitive changes and depression is not clear. The direct effect of INF may be on serotonergic neurotransmission. IDO which converts tryptophan into kynurenine may play an important role. IDO activation leads to reduced level of tryptophan, which is a precursor of serotonin (5-HT) and therefore decreased level of 5-HT in brain. Kynurenine metabolites such as 3-hydroxy-kynurenine (3-OH-KYN) and quinolinic acid (QUIN) have toxic effect on brain neurotransmission function. 3-OH-KYN leads to oxidative stress by increasing the production of reactive oxygen species (ROS), and QUIN may cause the overstimulation of hippocampal N-methyl-D-aspartate (NMDA) receptors, which leads to hippocampal atophy and cell death of brain. Peripheral kynurenine is transported through blood brain barrier by large neutral amino acid carriers and reaches the central nervous system, and finally taken up by glial cells. Finally neurotoxic metabolites are formed in the brain and leads to neurodegeneration (Marieke and Maes, 2004). INF treated patient shows two type of syndromes 1) mood or cognitive syndrome that appears late and responds to anti-depressant drugs and is linked mainly to decrease in serotonin metabolism 2) neurovegetative syndrome which presents characteristically with fatigue, psychomotor slowing and it appears early with initiation of therapy but alarmingly it does not responds to antidepressant medication the cause may be due to alteration in basal ganglia dopamine metabolism (Marieke and Maes, 2004). These correlations indicate towards the role of cytokine induced behavioral changes in diseased patients. It will not be obscure to say immune mediated cognitive and behavioral changes may be potential model in development of neuropsychiatry symptoms without medical illness and this should be further investigated.

Conclusion

Various studies done for association of increased secretion of cortisol and depression or cognitive changes suggest that severe life event may be a causative factor. However, this cannot stand alone as the cause of depression and cognitive changes. Furthermore in mild to moderate depression in the community may not be associated with hyper-secretion of cortisol. It suggested another causes to be causative factor. It was suggested with decrease level of brain 5HT functions associated with depression which requires further evaluation. Another cause includes decreased level of tryptophan which acts as precursor of 5HT. This did not gain importance as tryptophan was mainly available nutritionally and it is very unrealistic to say every undernourished subject will develop depression. Also the level of tryptophan causing changes is in 5HT activity not determined yet. Strikland *et al*. had correlated depression with stressful life event but not all developed depression with stressful life event. So, a bigger possibility lies with some genetic factor involved. Neurobiological changes

associated with dementia and depression needs to be investigated and explored more to correlate them. Individual response to stressful life event is different and so the chances of developing depression and cognitive changes later in life. Few studies also correlates immune response to depression which was evident in patients treated with interferon in hepatitis. An integrated model providing the actual explanation is needed which will provide the insight to break the viscous circle and help early diagnosis and treatment of cognitive changes and depression.

Declaration of intrest

None

REFERENCES

Bauer ME, Vedhara K, Perks P, *et al*. 2000. Chronic stress in caregivers of dementia is associated with reduced lymphocyte sensitivity to glucocorticoids. *Journal of Neuroimmunology*, 103, 84-92.

Cowen PJ 2002. Cortisol, serotonin and depression: all stressed out? *British Journal of Psychiatry*, 99,100.

Cowen PJ, Clifford EM, William C, *et al*. 1995. Why is dieting so difficult? *Nature*, 376, 557.

Da Roza Davis J.M & Cowen PJ. 2001. Biochemical stress of caring. Psychological Medicine, 31, 1475-1478.

Fenstorm & JD & Wurtman RJ. 1971. Brain serotonin content; physiology dependence on plasma tryptophan levels. *Science*, 173, 149-152.

Goodall EM, Cowen PJ, Franklin M, *et al*. 1993. Ritanserine attenuates anorectic, endocrine and thermic response to d-fenfluramine in human volunteers. *Psychopharmacology*, 112, 461-466.

Jensen MA, Yanowitch RA, Lee E, *et al*. 2003. Adrenocorticotropic hormone and α-melanocyte stimulating hormone induces indolamine 2,3-dioxygenase activity in monocytic cells. *American Neurology Association*.

Maes M, Jacobs MP, Suy E, *et al*. 1989. Cortisol, ACTH, prolactin and beta-endorphin response to fenfluramine administration in major depressed patients. *Neuropsychobiology*, 21, 192-196.

Marieke CW. And Maes M, 2004. The role of indolamine 2,3-dioxygenase (IDO) in pathophysiology of interferon-α-induced depression. *Journal of Psychiatry Neuroscience*, 29(1).7-11.

Mc Allister-williams, Anderson RH, RJ & Young AH. 2001. Brain serotonin$_{1A}$ receptor binding measured by positron emission tomography with [^{11}C] WAY-100635: effects of depression and antidepressant treatment. *Archives of General Psychiatry*, 57, 174-180.

Strikland PL, Deakin JFW, Percival C, *et al*. 2002. The bio-social origin of depression in the community. Interaction between social adversity, cortisol and serotonin neurotransmission. *British Journal of Psychiatry*, 180, 168-173.

Walsh AES, Oldman AD, Fralanklin M, *et al*. 1995. Dieting decreases plasma tryptophan and increases the prolactin response to d-fenfluramine in women butnot in men. *Journal of Affective Disorders*, 33, 89-97.

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