K. Nabe, et al. [2008] Med. Hypotheses Res. **4**: 79–83.

CLINICAL VIEWPOINT

Depression is a Component of the Metabolic Syndrome

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Abstract. Type 2 diabetes is known to be frequently associated with depression. It is reasonable to assume that diabetes may increase the risk for depression, and that depression may aggravate glycemic control. However, it is also possible that there may exist some common pathogenetic mechanisms of the two disorders, *ie* type 2 diabetes and depression. Several possible candidates for 'common soil' can be listed. First, hyperactivity of the hypothalamo-pituitary-adrenal axis may underlie type 2 diabetes and depression, as typically found in Cushing syndrome, which presents with both diabetes mellitus and depression. Second, there have been some preliminary evidences that decreased central serotonergic activity, which is considered to be responsible for depression, may result in insulin resistance. Third, some hypothalamic abnormality may underlie at least some portion of type 2 diabetes and metabolic syndrome. Based on those backgrounds, here we present a hypothesis that depression is one component of metabolic syndrome, and that antidepressant may improve glycemic control in type 2 diabetes. This hypothetical viewpoint may lead to the development of new drug for the prevention of metabolic syndrome.

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Received on 12-18-2007; accepted on 04-15-2008.

1. Introduction

It has been well known that type 2 diabetes is more frequently associated with depression than general population [1]. It is reasonable to assure that diabetes may increase the risk for depression, and that depression may aggravate glycemic control, considering that psychosocial stress induces hyperglycemia [2]. The presence of diabetes doubles the odds of comorbid depression in a meta-analysis [3]. It is to be noted that both depression and type 2 diabetes are increasing, especially in east Asia, including Japan [4], and the prevalence of the former appears to be in parallel with that of the latter in Asia [4,5]. Type 2 diabetes is generally considered to be based upon both insulin resistance and insulin deficiency, and metabolic syndrome has been recognized as a risk for insulin resistance [6]. Recently it has been reported that among middle-aged healthy women, depressive symptoms are associated with the cumulative prevalence and risk for developing the metabolic syndrome over 15 years [7]. Recently it is suggested that the change in central endocrine functions may underlie type 2 diabetes or metabolic syndrome [8]. On the other hand, the change in central hormonal activity may affect the higher brain function, as we proposed for central diabetes insipidus [9].

These finding prompted us to propose a hypothesis that metabolic syndrome and that depression may share common pathogenetic mechanisms.

2. Increased Activity of the Hypothalamo-Pituitary-Adrenal Axis

The hypothalamic-pituitary-adrenocortical (HPA) axis is an essential component of an individual's capacity to cope with stress. Excessive and sustained cortisol secretion (Cushing's syndrome) has been classically associated with depression, osteoporosis, immunosuppression, visceral obesity, insulin resistance, dyslipidemia, dyscoagulation, and hypertension, all of which share the spectrum of metabolic syndrome, along with their morbid sequelae of atherosclerosis and cardiovascular disease [1]. On the other hand, excessive stimulation of the axis induced by uncontrollable excess stress has been implicated in depression. Hyperactivity of the HPA axis is observed in the majority of the depression patients [10]. Depression has earlier been indicated to show elevated serum cortisol, loss of suppression on a low-dose dexamethasone suppression test, and a loss of the normal circadian rhythm of cortisol, which is called pseudo-Cushing state [11].

It is, therefore, possible that increased HPA axis activity may cause metabolic syndrome or type 2 diabetes as well as depression.

3. Centrally-decreased Serotonergic Activity

Second, central decreased serotonergic activity may be responsible for depression and type 2 diabetes [10]. The atypical antipsychotic agents which inhibit serotonergic neurotransmission have been reported to induce insulin resistance and diabetes [12]. The metabolic syndrome is reported to be associated with diminished brain serotonergic activity [13].

4. Hypothalamic Abnormality

Third, as we have recently proposed, it is possible that hypothalamic abnormality including HPA axis hyperactivity described above, may underlie at least some portion of type 2 diabetes or metabolic syndrome [8]. Although it remains to be elucidated to what extent hypothalamus is involved in pathogenesis of depression [10], it is plausible that some hypothamalic abnormality may underlie both depression and metabolic syndrome.

5. Clinical Implications

As described above, it has recently been reported that among women without the metabolic syndrome at the baseline, the risk for the metabolic syndrome varied from 1.21- to 2.12-fold for more severe depressive symptoms or very stressful life events, and psychosocial factors was an independent predictor of the risk for developing the metabolic syndrome by multiple definitions [7]. Therefore, depression may be considered as a novel risk factor for metabolic syndrome.

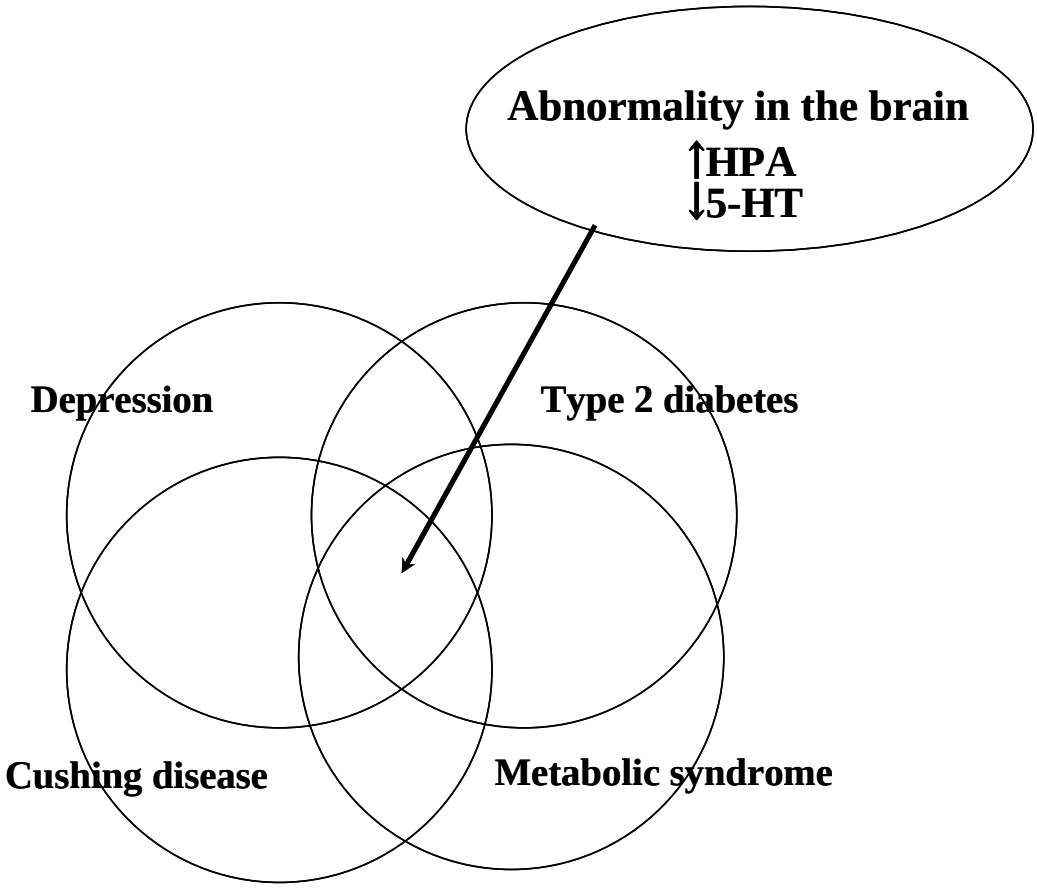

Figure 1. Hypothetical relationship between depression, Cushing's syndrome, metabolic syndrome, and type 2 diabetes.

As for the viewpoint of therapeutic strategy, there have been several evidences, which suggest that antidepressants can improve glycemic control in diabetic patients. Fluoxetine, the first selective serotonin reuptake inhibitors (SSRIs), was reported to reduce effectively the severity of depression in diabetic patients, to produce a trend toward better glycemic control after eight weeks [14], and to improve insulin-mediated glucose disposal in obese patient with type 2 diabetes independently of weight loss [15]. Fluoxetine was also effective to decrease fasting blood glucose level of patients with major depressive disorder [16], and fluoxetine-treated subjects showed a greater decrease in total daily insulin dose [17]. Treatment with paroxetine, another SSRI, resulted in an increase in sex-hormone-binding-globulin levels as a sign of improved insulin sensitivity in mildly depressed women with non-optimally controlled type 2 diabetes [18]. It has been also reported that omega-3 polyunsaturated fatty acids, e.g. eicosapentaenoic acid, was effective to decrease occurrence of both depression and type 2 diabetes [19], and that bupropion was effective to treat depression and improve glycemic control in diabetic subjects associated with major depression [20].

Furthermore, it has very recently been reported that fluvoxamine, another SSRI, in combination with a 5-HT_{2C} receptor inactivation, induces appetite-suppressing effect in mice via 5-HT1B receptors through up-regulation of hypothalamic pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript gene expression and down-regulate hypothalamic orexin gene expression in mice [21]. This result suggests

that some SSRI may have another benefit to reduce appetite in diabetic subjects, although there has been no evidence in humans yet.

6. Suggestions for the Experimental Testing of our Hypothesis

To test our hypothesis presented here, further investigations are needed to examine the prevalence of depression in metabolic syndrome patients in comparison with those without metabolic syndrome. Furthermore, it is of clinical significance to investigate whether depression can be an independent risk factor for morbidity and mortality from cardiovascular diseases in metabolic syndrome, and also to examine whether the use of antidepressants will improve glycemic control in subjects with depression and type 2 diabetes in a randomized clinical trial.

7. Summary

Here we presented a hypothesis suggesting that depression is one of the components of the metabolic syndrome, and that the use of antidepressants may improve glycemic control in type 2 diabetes. We believe this hypothetical viewpoint may also lead to the development of new drugs and therapies for the control, treatment and prevention of the metabolic syndrome.

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