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Editorial

'Let food be thy medicine, and medicine be thy food': Hippocrates revisited

The omniscient Hippocrates, who lived around 400 BC, theorised that physiological abnormalities and environmental factors such as diet might be the root of mental disorders. Today, we are just about to realise that this, to some degree, may indeed be the case.

Metabolic disorders such as obesity, metabolic syndrome and diabetes type II are reaching epidemic proportions in many parts of the world as an inevitable attendant of the prevailing sedentary lifestyle and excess caloric intake (1,2). Similarly, major depressive disorder is a serious and common disease with debilitating consequences for the individual and great costs for the society (3). Recent meta-analyses have shown that major depressive disorder is an independent risk factor for metabolic syndrome and diabetes type II, and vice versa (4–6). Importantly, increased cardiovascular morbidity and mortality are seen not only in diabetes type II, but also in major depressive disorder (7–10). Furthermore, increased visceral obesity is reported in depressed individuals (11–13).

A number of possible explanations for the association between metabolic syndrome/diabetes type II and major depressive disorder exist. Adverse traits in lifestyle are well described in depressed individuals (14,15), but it remains to be elucidated whether some pathophysiological mechanisms could be shared as well.

Interestingly, it is known from the literature that intrauterine growth restriction and, in turn, low birth weight are associated with later life metabolic disorders (16–18). An altered hypothalamic–pituitary–adrenal axis regulation may be involved, as clinical studies have called attention to an important role of the hypothalamic–pituitary–adrenal axis, especially in visceral obesity (19–22). Winding up this hypothetical causative assumption, intrauterine growth restriction is indeed associated with increased cortisol levels and hypothalamic–pituitary–adrenal axis responsivity (23,24). As it is well established that imbalances in the hypothalamic–pituitary–adrenal axis may be a turning point in the development of major depressive disorder, as well as other psychiatric illnesses, this calls for special attention.

In this issue, Abildgaard et al. (25) present a study on male rats that were subjected to prenatal stress (intrauterine growth restriction induced by maternal dexamethasone treatment) and given a high-fat diet for 8 weeks. Interestingly, the high-fat diet approximately doubled the corticosterone response to acute restraint stress in these rats independently of the intrauterine growth restriction. Importantly, these findings suggest that influencing environmental factors may be of greater significance compared with prenatal stress and intrauterine growth restriction in regulation of the neuroendocrine stress response and point out a possible role of the hypothalamic–pituitary–adrenal axis in metabolic disorders.

As a subgroup of patients suffering from depressive disorder consistently presents with the impaired ability of dexamethasone to suppress the hypothalamic–pituitary–adrenal axis (26), it was rendered probable many years ago that hypothalamic–pituitary–adrenal axis disturbances in depression may lead to secondary metabolic disorders (27,28). Vice versa, Abildgaard et al. (25) show that high-fat diet and prenatal dexamethason exposure concomitantly exacerbated depressive-like behaviour in the animals. Taken together, this may imply a bidirectional association between metabolic disorders and depression mediated by the hypothalamic–pituitary–adrenal axis.

A new class of drugs may turn out to be attractive in this context, namely, inhibitors of 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1). Inhibition of this enzyme may prevent conversion of the biologically inactive cortisone into active cortisol locally into different tissues including the adipose tissue. Preclinical and clinical studies suggest a modest positive effect on metabolic parameters (29–32), but further studies are needed to conclude on whether the 11β-HSD1 inhibitors could also reduce the risk for developing comorbid depression.

Another novel area of great relevance is the gut microbiota that has just recently been shown to affect a broad range of physiological systems, especially within the field of obesity and insulin resistance (33–35). Intriguingly, studies on experimental animals have proven that ingestion of certain live bacteria (probiotics) may affect behaviour and hypothalamic–pituitary–adrenal axis activity (36–40). In a clinical study, 30 days of probiotic supplementation improved anxiety- and depression-related rating scales and decreased urinary cortisol excretion compared with baseline in healthy humans (36).

The present evidence may remind us that the body works as a whole and that psychiatric disorders should not only be seen as the result of localised disease processes in the brain such as specific neurochemical abnormalities. More likely, a complex crosstalk between the brain and periphery takes place. Keeping this perspective in mind when designing research experiments may turn out to provide us with a better understanding of psychiatric–somatic comorbidities in addition to new groundbreaking findings and novel principles of treatment.

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