Major Depressive Disorder

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Introduction to Depressive Disorders

Depression affects about 121 million people worldwide and is characterized by episodes of affective, somatic, cognitive, and motivational symptoms generally expressed by loss of interest and pleasure with increasing functional impairment, morbidity, and mortality.

Depressed patients die earlier [1] as they show increased risk of cardiovascular disease (CVD) [2] and significant increases in suicide [3]. Interestingly, the association between depression and CVD is likely mediated by metabolic syndrome (MetS, see chapter "Metabolic syndrome"). Depression clearly correlates with MetS, which is likely the cause for premature CVD. The correlation is bidirectional, as occurrence of depressive episodes is increased in Mets, and symptoms and occurrence of MetS (most commonly visceral obesity and dyslipidemia) are increased in depression [4].

Several subtypes of depression exist, with major differences in metabolic outcome of the disease, i.e., melancholic, atypical, and undifferentiated type. Melancholic depression is generally characterized by anhedonia (from Greek, without pleasure) and is worse in the morning. It often includes lack of reactivity to pleasurable stimuli, psychomotor also retardation or agitation, loss of appetite or weight, and insomnia. In contrast, atypical depression is worse in the evening and is defined by mood reactivity (mood brightens in response to positive events), appetite and weight increase, and hypersomnia.

Etiology of major depression is still largely unknown, although it is likely associated with the endogenous stress response. Stress response involves several neurotransmitters, such as serotonin (5-hydroxytryptamine, 5-HT), catecholamines (such as norepinephrine (NE), dopamine (DA) and histamine with a stated role in regulation of mood and behavior. Additionally, exposure to prolonged, inescapable stress causes activation of the hypothalamic-pituitary-adrenal (HPA) and sympathoadrenal axis. HPA activation can promote inflammatory response, thus increasing proinflammatory cytokines and production of nitric oxide and reactive oxygen species (ROS), which lead to neuro-metabolic disturbances that are likely involved in the generation of depressive episodes. Inflammation, disturbance of the autonomic nervous system, and neurotransmitter defects are all implicated in depression (Fig. 1) and may cause major metabolic disturbances.

Pathophysiology of Depressive Disorders and Metabolic Alterations

Although a common origin for the different subtypes of depression is likely, they do differ in metabolic outcome and phenotypes. Patients

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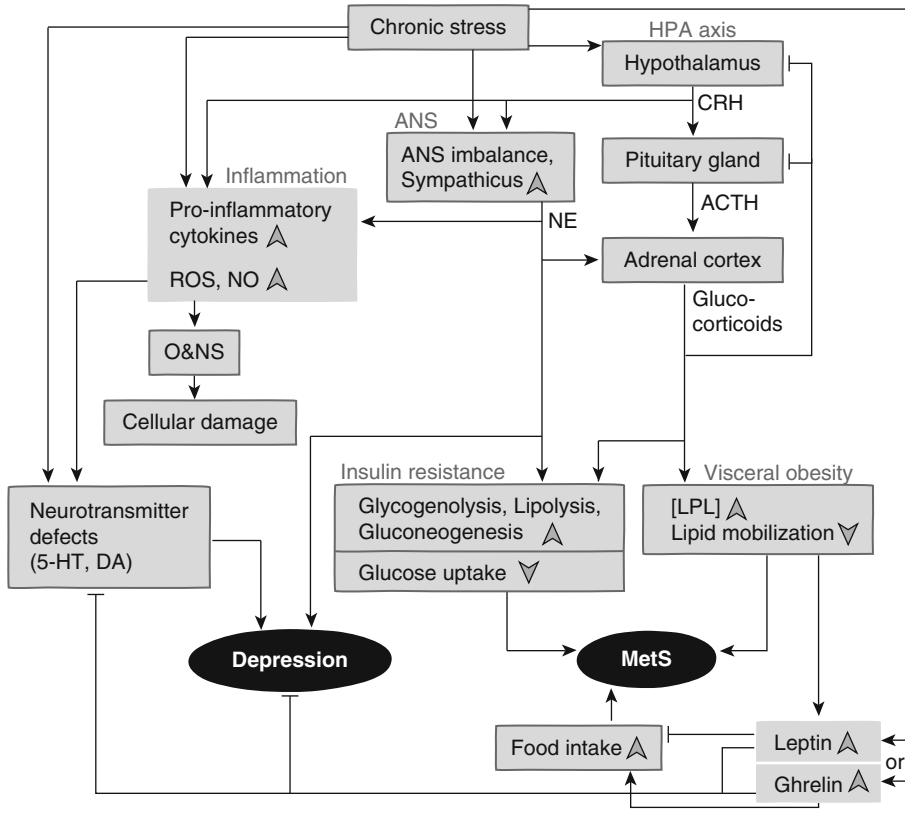

Fig. 1 Pathophysiological overlap between depression and metabolic syndrome. Depression and metabolic syndrome (*MetS*) share common pathways in the stress system, involving an abnormal activation of the hypothalamus-pituitary-adrenal (*HPA*) axis and an imbalance of the autonomic nervous system (*ANS*). In both conditions, a low-grade systemic inflammation manifests, which leads to enhanced oxidative and nitrosidative stress (*O&NS*). An antidepressant efficacy has been demonstrated for leptin and ghrelin, two peripheral hormones classically implicated in the homeostatic control of food intake. *NE* norepinephrine, *5HT* serotonin, *DA* dopamine, *CRH* corticotropin-releasing hormone, *ACTH* adrenocorticotrophic hormone, *ROS* reactive oxygen species, *NO* nitric oxide, *LPL* lipoprotein lipase

with atypical and undifferentiated depression show more appetite and subsequently more total and abdominal fat, whereas melancholic patients show reduced weight. It should also be noted that depression has a higher prevalence in women and their health-related risks are likely different than in men. As women tend to react to depressive episodes by hyperphagia, whereas men tend to consume alcohol [5], they show an increased risk for adiposity and thus MetS [6].

Several intra- and extracerebral metabolic pathways are changed during depression, which are discussed below.

Monoamine Systems

The monoamine hypothesis of depression postulates a pathogenic role for disturbances in the monoaminergic systems, involving not only NE, 5-HT, and DA but also excitatory and inhibitory amino acids, receptor families, and second messengers. In animal models of chronic stress, neurobehavioral responses are associated with perturbations in monoamines transmission. Reduction in NE neurotransmission from the locus ceruleus to the limbic system and the cortex may explain anergia, anhedonia, and diminished libido. 5-HT transmission is

decreased, due to the depletion of 5-HT stores and increased negative feedback via autoreceptors. Finally, the reduced mesocortical and mesolimbic DA transmission may account for the motivational, cognitive, and motor alterations of depression.

HPA Axis

Increased HPA activity is present in 20–40 % of depressed inpatients as documented by anatomic, responsive, and biomarker changes (e.g., adrenal and pituitary enlargement, enhanced adrenal response, and increased plasma cortisol levels, respectively). Acute stress triggers the release of corticotropin-releasing hormone (CRH) from the hypothalamus. CRH activates synthesis and release of adrenocorticotrophic hormone (ACTH) from the anterior pituitary, which, in turn, triggers release of cortisol and other glucocorticoids from the adrenal cortex. CRH also enhances proinflammatory cytokines and decreases protective neuropeptides [7].

The glucocorticoids hypothesis proposes that melancholic depression results from hyperactivity of CRH neurons, while atypical depression would be based upon increased levels of peripheral corticosteroids, which subsequently suppress CRH (hypoactive HPA axis) [8]. Under acute stress, glucocorticoids mobilize energy for the body's "fight-or-flight" response via gluconeogenesis, glycogenolysis, and lipolysis. Under chronic stress, however, allostatic effects are observed, as the HPA axis is chronically activated and glucocorticoid levels are stably elevated. This activates lipoprotein lipase in visceral fat depots, which accumulates triglycerides in the visceral area (see chapter "Hyperlipidemia") [9]. Increased generation of cortisol from cortisone in visceral fat further amplifies this effect and thus visceral adiposity. Chronically elevated glucocorticoids also contribute to insulin resistance and diabetes, by reducing the translocation of glucose transporters (in particular GLUT4) to the cell surface (see chapter "Diabetes mellitus").

Autonomic Nervous System

An imbalance favoring sympathetic over parasympathetic activity is a consistent finding in depression (likely caused by chronic stress as well). Heightened sympathetic activity may be mediated by increased NE metabolites [10]. Release of CRH from the hypothalamus and NE from the locus ceruleus coordinates the stress response. Increased sympathetic activity often leads to/causes higher resting heart rates, diminished heart rate variability, and baroreflex dysfunction. It is also proposed to elevate serum insulin and decrease insulin sensitivity [11]. Sympathetic activation enhances release of catecholamines, which increase insulin resistance by reducing uptake of glucose into muscle and subcutaneous fat cells, stimulate release of free fatty acids from fat cells, and increase production of glucose in the liver (via glycogenolysis and gluconeogenesis) [12].

A disturbance in the sympathetic/parasympathetic equilibrium is likewise found in MetS. In healthy individuals, the autonomic balance oscillates between active (catabolic) and inactive (anabolic) periods. In conditions of increased energy intake, parasympathetic activity is increased, in particular in the abdominal compartment, resulting in increased insulin secretion and growth of intra-abdominal fat tissue [13]. On the other hand, due to sedentary lifestyle, sympathetic activity remains high in the skeletal muscle, thus reducing blood flow and glucose uptake by the muscle cells.

Inflammation

According to the cytokine hypothesis, depression is associated with immunological disturbances, especially increased production of proinflammatory cytokines by lymphocytes. A chronic, systemic low-grade inflammation is found in depression, including cell-mediated immune activation (see chapter "Overview" under part "Immune system") and activation of interferon γ-related pathways [14]. Levels of proinflammatory cytokines, particularly interleukin-1, interleukin-6, tumor necrosis factor-α (TNF-α;

see also chapter "Diabetes mellitus"), and cell-mediated macrophage activation, are increased. Interestingly, these cytokines induce degradation of tryptophan, thus reducing the availability of tryptophan and 5-HT. They also inhibit the action of lipoprotein lipase, inducing dyslipidemia (see chapter "Hyperlipidemia"), and prevent vasodilatation of resistance vessels, predisposing to hypertension (see chapter "Hypertension") [15]. Furthermore, TNF-α impairs the function of the insulin receptor and insulin receptor substrate 1 via their phosphorylation, thus contributing to insulin resistance.

Oxidative Stress

Chronic inflammation depletes the storage of endogenous antioxidants and increases ROS levels, which activate proinflammatory genes. This vicious cycle is called the inflammatory and nitrosidative pathway and leads to increased neurodegeneration [16] and β-cell toxicity. The central nervous system is particularly vulnerable to oxidative stress due to its low expression of antioxidant enzymes (characteristics it shares with pancreatic β-cells), as well as its high content of polyunsaturated fatty acids. Moreover, oxidative stress alters intracellular signaling, most importantly Akt (also called protein kinase B) in the liver leading to aberrant output of glucose and triglycerides. Perturbations in Akt activity are accompanied by impaired insulin-stimulated glucose transport in muscle and adipocytes.

Peripheral Hormones Leptin and Ghrelin

Leptin is secreted by adipocytes and acts on the hypothalamus to reduce appetite and eating (see chapter "Diabetes mellitus"). However, obesity induces a state of leptin resistance. As leptin is also involved in mood regulation with an antidepressant effect [17], leptin resistance could underlie depressive symptoms. Thus, the leptin hypothesis of depression is complementary to previous hypotheses. Leptin receptors are present on 5HT and DA neurons, allowing leptin to modulate the release of these monoamines. Leptin is also known to decrease the release of corticosteroids during the stress response via the HPA axis.

Ghrelin is a gut-derived hormone, which induces a potent feeding response via its receptors in the hypothalamus, and probably mediates hyperphagia in response to stress [18]. Since ghrelin administration produces antidepressant responses, it has been postulated that it helps the organism to cope with stress. In addition, it also activates the dopaminergic reward circuitry, while reinforcing the search for palatable sweet food. Thus, depressed patients may be more susceptible to so-called "Stress eating" [19].

Association Between Depressive Symptoms and MetS

To date, the exact mechanisms linking MetS to depression are unclear. MetS could be due to the unhealthy lifestyle habits of depressed patients, as it is reduced after adjustment of smoking status, alcohol use, and especially body mass index [20]. However, specific dyslipidemic changes remain associated with corresponding depression subtypes [20]. As it is apparent from the previous sections, MetS and depression share common alterations of the stress system (HPA, inflammation, ROS), indicating a common pathophysiologic mechanism (Fig. 1).

Treatment of Depressive Disorders

Nowadays, several classes of antidepressants are available: tri- and tetracyclic antidepressants (TCAs); selective reuptake inhibitors for 5-HT (SSRIs), NE (NRIs), both 5-HT and NE (SNRIs), and both NE and DA (NDRIs); as well as 5-HT antagonist/reuptake inhibitors (SARIs).

TCAs, named after their chemical structure (e.g., imipramine, amitriptyline), and SSRIs (e.g., fluoxetine, fluvoxamine, citalopram) are still common in pharmacological treatment of depression, with SSRIs becoming favored over TCAs due to fewer side effects (see below).

The general mechanism of TCAs and the reuptake inhibitors is to prevent presynaptic reuptake of monoamines (5-HT, NE, DA), thus increasing their activity in the synaptic cleft. In particular, they ameliorate depressed mood, psychomotor retardation, and suicidal ideation, whereas sleep disturbances, concentration deficits, and lack of interest usually persist. However, acutely enhanced levels of neurotransmitters may lead to adaptive desensitization of postsynaptic neurotransmitter receptors.

Key to management and treatment of depression is the reduction or avoidance of depressive episodes. Yet, metabolic derangements that underlie both depression and MetS should also be screened and targeted, including eating patterns, thyroid dysfunction, body mass index, and fasting blood glucose. These risk factors should also be considered a primary therapeutic target. In mild cases, dietary [21] and exercise [22] intervention improve anxiety, depression, and affective symptoms especially in obese patients, probably normalizing derangements in the HPA axis, peripheral hormones, and inflammation. Furthermore, as additive treatment options, cortisol synthesis inhibitors could dampen the hyperactive HPA axis; anti-inflammatory drugs could decrease inflammatory and nitrosidative pathway-induced damage [16]; and the antidiabetic drug metformin could exert neuroprotective, neurotrophic, and anti-inflammatory effects [23].

Influence of Treatment on Metabolism

Several psychotropic drugs are associated with adverse metabolic effects [24] that should be taken into account, especially when dealing with patients with metabolic comorbidity [25].

The classic TCAs, albeit efficacious, exert many undesired pharmacological actions. For example, they block histamine 1 receptors, potentially explaining associated weight gain and dyslipidemia. TCAs may also interfere with insulin secretion, blocking M3 muscarinic acetylcholine receptors in β-cells [26]. TCAs also activate peripheral α1 adrenergic receptors, contributing to hypertension (see chapter "Hypertension") [27].

SSRIs show a more favorable tolerability profile because of their selectivity. However, increased availability of 5-HT may have negative effects as it regulates a multitude of functions, such as sleep, sexual function, and appetite, showing adverse effects on quality of life. Although a weight loss has been observed during early treatment, long-term therapy is associated with significant weight gain.

Perspectives

It is predicted that by the year 2020, depression will be the second leading cause of death after CVD. Thus, further targets, possibly within the inflammatory and nitrosidative pathways, should be considered for the treatment of depression in the future: proinflammatory cytokines and their receptors, intracellular inflammatory mediators, glucocorticoid receptors, and neurotrophic factors.

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