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Treat the brain and treat the periphery: toward a holistic approach to major depressive disorder

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The limited medication for major depressive disorder (MDD) against an ever-rising disease burden presents an urgent need for therapeutic innovations. During recent years, studies looking at the systems regulation of mental health and disease have shown a remarkably powerful control of MDD by systemic signals. Meanwhile, the identification of a host of targets outside the brain opens the way to treat MDD by targeting systemic signals. We examine these emerging findings and consider the implications for current thinking regarding MDD pathogenesis and treatment. We highlight the opportunities and challenges of a periphery-targeting strategy and propose its incorporation into a holistic approach.

Introduction

Major depressive disorder (MDD) has become one of the world's leading causes of disease burden and disability [1]. The substantially high prevalence and social impact of MDD worldwide are serious concerns in light of the limited number of antidepressant treatments [2]. Moreover, the clinical management of MDD is increasingly complicated by its idiopathic pathogenesis and comorbidity with a constellation of somatic disturbances such as diabetes and cancer [3]. These complexities are presenting an array of challenges to current fragmentary knowledge about MDD pathogenesis and treatment strategies.

The 'monoamine hypothesis' has prevailed in the pipeline of antidepressant discovery for decades [4] and, more recently, there has been considerable interest in targeting the *N*-methyl-D-aspartate (NMDA) glutamate receptor, synaptic and epigenetic mechanisms [5–7]. Although these neurobiological insights are providing novel pathological understandings at the molecular, cellular and circuit level, they still have limitations and cannot explain the inadequate drug response in a substantial proportion of depressed patients. In addition, simple manipulation of these central targets seems insufficient to tackle the heterogeneous and multisystem comorbid nature of depressive symptoms [8].

Despite the overall frustrations, the growing appreciation of the complexity of MDD offers much more than challenges. In fact, an evolving systems-level understanding of MDD has led to a series of truly remarkable findings on the close coupling between systemic signals and depressive symptoms that open a new dimension to understanding MDD. Meanwhile, the expanding knowledge of peripheral signals in dictating the psychiatric and behavioral deficits has set in motion a re-thinking about what the current neurocentric paradigm is missing in the pursuit of more-efficacious, fast-acting and safer therapies [9–11]. This review focuses on the emerging peripheral targets for treating MDD as a systems disorder, highlighting the integration of a periphery-targeted intervention strategy into the current knowledge of MDD treatment as a viable path ahead. The promises and key questions for the clinical translation to MDD therapy are discussed, with the proposal for a holistic approach to move the field forward.

Systems regulation of MDD

MDD has emerged as a multiorgan disorder with psychological and somatic disturbances [12]. The complex disease network notably consists of a myriad of regulatory signals at the systems level, which mount a close interaction with multiple central pathways relevant to mood regulation such as monoamine

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metabolism, neuroendocrine function and synaptic plasticity. These accumulating findings have been covered by several excellent reviews [10,13,14]. Herein, only recent research progress is briefly outlined, which, in conjugation with previous reports, constitutes the basis to force a reappraisal of the conventional wisdom.

Clinical and experimental evidence

The early notion of systems regulation of MDD is supported by several clinical observations: (i) clinical risk factors or comorbid diseases for MDD (e.g. cancer, diabetes and inflammatory bowel disease) invariably involve a physiological or immune disturbance at the systems level; (ii) depressive symptoms could arise from the exposure to cytokines or immunoregulatory drugs, as is commonly seen with interleukin (IL)-2 or interferon-alpha treatment [13]; (iii) markers of ongoing inflammation or metabolic imbalance in the plasma can become attenuated with antidepressant therapy [15]. These cardinal observations are followed by intensive attention to systems inflammatory factors for MDD and the therapeutic effects of targeted therapies [16,17]. Recently, a growing interest, in particular, is seen on the effect of psychosocial stress on systems inflammation and metabolism [9,18], which has been proposed as a novel player in linking the brain dysfunction and somatic symptoms of mood disorders.

More causal evidence for the systemic control of MDD has come from experimental findings. For example, direct inflammatory or immune challenges to the blood or peripheral organs, or modeling the chronic inflammatory states with high-fat diet or endotoxin, produce behavioral symptoms in animals [10,19]. Also, there is converging evidence that suggests blocking the cytokine actions in the periphery could ameliorate depression-like behaviors [20]. All these findings provided the impetus for recent research efforts to seek in-depth molecular mediators bridging the periphery–brain interaction in psychiatric disorders. In this regard, one of the most rapid-growing and active fields is the illumination of the gut microbiome as a master regulator of MDD and many other brain disorders [21], which also strengthens the early 'hygiene hypothesis' of MDD that states that a changing microbial environment is implicated in the inflammatory imbalance observed in mental disturbance [22].

Evolving mechanistic understanding

In essence, multiple, neural, endocrine, immune and metabolic signaling mechanisms provide the basis for systemic regulation of brain health and disease (Fig. 1). The close interactions among these operating pathways constitute the backbone of current mechanistic knowledge about MDD pathogenesis at the systems level.

The neuroimmune crosstalk provides the major route for systemic immune mediators to act directly or indirectly on the central nervous system (CNS). Along this pathway, the recognition of bacterial products or cell-damage-associated components by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) is a central event in transmitting immune responses or neural signals to the distal brain regions. This is highlighted in a recent theory implicating the NOD-like receptor protein (NLRP)3 inflammasome as a key mediator linking psychological stress, comorbid systemic disturbance and psychiatric distress [18]. Moreover, the

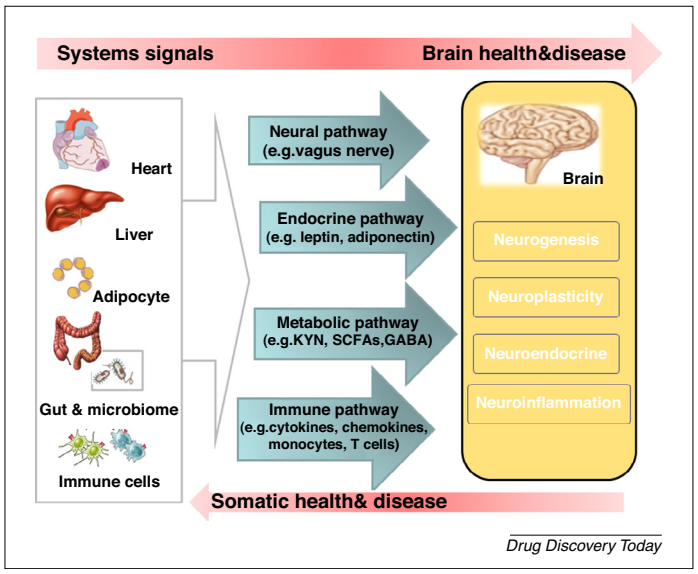

FIGURE 1

Major signaling pathways underlying the systems control of brain health and disease. The pathophysiology of the brain is closely coupled with multiple organs in the periphery, and *vise versa*, attributed to the existence of a bidirectional crosstalk mechanism at the systems level. The periphery–brain communication is typically mediated by neural, endocrinal, metabolic and immune pathways. In this manner, the peripheral system could exert a remote control over neurogenesis, neuroplasticity, neuroendocrine and neuroinflammation events, and thereby play an important part in dictating a healthy or dysfunctional brain. *Abbreviations*: KYN, kynurenine; SCFAs, short-chain fatty acids; GABA, γ-aminobutyric acid.

mediators involved in cell–cell interactions are important players. For example, P-selectin-mediated monocyte–cerebral endothelium interactions have recently been revealed as a crucial link between peripheral organ inflammation and sickness behaviors [23]. Similarly, the chemokine signals in orchestrating the recruitment of circulating immune cells also have essential roles.

The flow of metabolic signals, which are closely coupled with immune parameters, opens another interactive route. In this regard, the kynurenine pathway of tryptophan metabolism, which is sensitive to stress and immune triggers, stands in a unique position to mediate the effects of environmental factors on cognition and behavior. Another notable example is the master regulation of metabolic signals at the systems level by the gut microbiota, which, in concert with their immunomodulatory effects, collectively fosters capacity to affect remote brain development and function. Importantly, the existence of the microbiome–gut–brain axis serves as a bidirectional link between host factors (e.g. diet, stress, illness) and mood and behavior.

Emerging novel targets from the periphery

Gut microbial dysbiosis

Research on the role of gut microbiota in mental disorders has greatly enriched our knowledge about the impact of host–microbiome commensalism and dysbiosis on distal brain functions, which also fuel huge interest in targeting the co-existing microorganisms as a tractable strategy to the prevention and/or treatment of mental disorders [21,24]. For MDD, pre- and pro-biotic formulations and dietary interventions have been proposed as novel therapeutics to this debilitating disease [25,26]. For example,

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