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Review

Is serotonin an upper or a downer? The evolution of the serotonergic system and its role in depression and the antidepressant response

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ABSTRACT

The role of serotonin in depression and antidepressant treatment remains unresolved despite decades of research. In this paper, we make three major claims. First, serotonin transmission is elevated in multiple depressive phenotypes, including melancholia, a subtype associated with sustained cognition. The primary challenge to this first claim is that the direct pharmacological effect of most symptom-reducing medications, such as the selective serotonin reuptake inhibitors (SSRIs), is to increase synaptic serotonin. The second claim, which is crucial to resolving this paradox, is that the serotonergic system evolved to regulate energy. By increasing extracellular serotonin, SSRIs disrupt energy homeostasis and often worsen symptoms during acute treatment. Our third claim is that symptom reduction is not achieved by the direct pharmacological properties of SSRIs, but by the brain's compensatory responses that attempt to restore energy homeostasis. These responses take several weeks to develop, which explains why SSRIs have a therapeutic delay. We demonstrate the utility of our claims by examining what happens in animal models of melancholia and during acute and chronic SSRI treatment.

Contents

Abbreviations: 5-HT, 5-hydroxytryptamine (serotonin); DA, dopamine; NE, norepinephrine; ADM, antidepressant medication; SSRIs, selective serotonin reuptake inhibitors; SERT, serotonin transporter; 5-HIAA, 5-hydroxyindoleacetic acid; PFC, prefrontal cortex; mPFCv, ventral part of the rodent medial prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; VLPFC, ventrolateral prefrontal cortex; DRN, dorsal raphe nucleus; PET, positron emission tomography; ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; NET, norepinephrine transporter; DAT, dopamine transporter.

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1. Introduction

Depression is a heterogeneous suite of states characterized by sad mood and *anhedonia* (an inability to experience pleasure) (Hyman, 2010; Insel and Charney, 2003). Depressive states share some genes and neurobiology in common, but they otherwise differ in symptom and etiology (Akiskal and Akiskal, 2007; Dantzer et al., 2008; Flint and Kendler, 2014; Lux and Kendler, 2010; Maier and Watkins, 1998; Parker, 2000; Raison and Miller, 2013; Sullivan et al., 2012). For instance, depressive symptoms can occur in response to infection (called *sickness behavior*) or starvation (Hart, 1988; Keys et al., 1950), though the symptoms are not considered pathological in these contexts (Andrews and Durisko, in press; Dantzer, 2001; Engel and Schmale, 1972). In the fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5), the diagnostic category of major depression envelops some of the symptomatic heterogeneity by allowing for variability in weight, sleeping, and psychomotor activity (Table 1) (APA, 2013).

Episodes of major depression may be further subdivided into more precise phenotypes. Melancholia (weight loss, insomnia, and agitation/retardation) is considered by many to be the "biological core of depression" (Akiskal and Akiskal, 2007, p. 46). It is the most common and reliably diagnosed subtype, often accounting for 50% or more of clinical episodes (Angst et al., 2007; Taylor and Fink, 2008; Xiang et al., 2012). Melancholia is associated with heightened hypothalamic-pituitary-adrenal (HPA) activity (Taylor and Fink, 2008), which is a physiological indicator of stress (Chrousos, 2009). While it was formerly called *endogenous depression*, melancholia is in fact associated with stressful life events that are often serious or highly private in nature (Harkness and Monroe, 2002; Leff et al., 1970; Mundt et al., 2000; Willner et al., 1990). Atypical depression (weight gain, hypersomnia, and retardation) is the other major subtype, but it is heterogeneous and not well understood (Stewart et al., 2007).

Despite decades of research, the role serotonin plays in depressive phenotypes has not been conclusively determined. The original clue that monoamines (serotonin, norepinephrine, and dopamine) were involved in depression came from two serendipitous discoveries (Baumeister et al., 2003; Valenstein, 1998). First, during the investigations of iproniazid as a treatment for tuberculosis and imipramine as a treatment for schizophrenia, clinicians reported that these drugs could reduce depressive symptoms. An effort was then made to find a common pharmacological property that could explain their antidepressant effect. Eventually, researchers found that iproniazid inhibits the enzymes that breakdown the monoamines, while imipramine blocks the serotonin transporter (SERT) and the norepinephrine transporter (NET). Second, clinical observations suggested that reserpine, a drug known to deplete monoamines, increased depressive symptoms. These findings appeared to solve the puzzle. By preventing the breakdown of norepinephrine and serotonin, or preventing their clearance from the synapse, iproniazid and imipramine appeared to increase forebrain monoamine levels. The monoamine-enhancing effect of antidepressant medications (ADMs), coupled with the depression-inducing effects of reserpine, suggested that depression was caused by reduced monoamine neurotransmission (Everett and Toman, 1959; Jacobsen, 1964; Schildkraut, 1965).

Other researchers soon suggested that serotonin was the most important monoamine (Coppen, 1967). Often it is called the 'monoamine hypothesis' or the 'serotonin hypothesis.' We refer to it as the *low serotonin hypothesis* because it proposes a particular direction. Researchers then focused on the creation of drugs that could increase synaptic serotonin without perturbing other monoamines by selectively binding to the serotonin transporter (SERT). This research effort was successful, and the selective