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The catecholaminergic–cholinergic balance hypothesis of bipolar disorder revisited

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ABSTRACT

Bipolar disorder is a unique illness characterized by fluctuations between mood states of depression and mania. Originally, an adrenergic–cholinergic balance hypothesis was postulated to underlie these different affective states. In this review, we update this hypothesis with recent findings from human and animal studies, suggesting that a catecholaminergic–cholinergic hypothesis may be more relevant. Evidence from neuroimaging studies, neuropharmacological interventions, and genetic associations support the notion that increased cholinergic functioning underlies depression, whereas increased activations of the catecholamines (dopamine and norepinephrine) underlie mania. Elevated functional acetylcholine during depression may affect both muscarinic and nicotinic acetylcholine receptors in a compensatory fashion. Increased functional dopamine and norepinephrine during mania on the other hand may affect receptor expression and functioning of dopamine reuptake transporters. Despite increasing evidence supporting this hypothesis, a relationship between these two neurotransmitter systems that could explain cycling between states of depression and mania is missing. Future studies should focus on the influence of environmental stimuli and genetic susceptibilities that may affect the catecholaminergic–cholinergic balance underlying cycling between the affective states. Overall, observations from recent studies add important data to this revised balance theory of bipolar disorder, renewing interest in this field of research.

1. Introduction

Bipolar disorder is a debilitating neuropsychiatric illness that affects approximately 1% of the global population (Merikangas et al., 2011). A fundamental and distinctive characteristic of bipolar disorder is its cyclical nature involving switches between periods of mania and depression, distinguishing it from other psychiatric disorders such as schizophrenia and major depressive disorder. Symptoms of mania include elevated or irritable mood, hyperactivity, racing thoughts, less need for sleep, grandiosity, and sometimes psychotic symptoms. Depression is largely associated with symptoms seemingly opposite to those of mania, such as sad mood, poor self-esteem, insomnia, lethargy or feeling 'slowed down', and anhedonia (DSM-V, 2013). Despite the availability of a broad range of antipsychotics, antidepressants, and mood stabilizers, the treatment of bipolar disorder remains inadequate and an unmet public health need. Together with the multifaceted symptomatology, about a third of bipolar disorder patients attempt suicide (Novick et al., 2010), and the associated mortality rate from suicide attempts is high in this population (Osby et al., 2001). A better understanding of the mechanisms underlying the specific states of mania and depression could improve development of targeted therapies and ultimately benefit patients.

2. The original adrenergic–cholinergic balance hypothesis of mania and depression

Several decades ago, an adrenergic–cholinergic balance hypothesis was first postulated, proposing that the underlying mechanisms of mania reflect an imbalance of high adrenergic activity, whereas depression is a state caused by relative high cholinergic compared to adrenergic activity (Janowsky et al., 1972). Evidence for the involvement of central acetylcholine in the

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regulation of depression arose from reports of cholinergic agonists and acetylcholinesterase inhibitors inducing severe depression in humans and antagonizing symptoms of mania (Janowsky et al., 1994). These compounds increase central cholinergic tone because acetylcholinesterase is the primary enzyme responsible for breaking down acetylcholine throughout the nervous system. Various acetylcholinesterase inhibitors (Gershon and Shaw, 1961; Rowntree et al., 1950; Bowers et al., 1964), including physostigmine (Janowsky et al., 1973b; Modestin et al., 1973b, 1973a; Janowsky et al., 1974; Davis et al., 1978; Oppenheim et al., 1979; Risch et al., 1981) have been reported to induce symptoms of depression in human subjects. Other agents that induce depression are the direct cholinergic muscarinic receptor agonist arecoline (Nurnberger et al., 1983), the non-selective muscarinic receptor agonist oxotremorine (Davis et al., 1987), and acetylcholine precursors including deanol, choline, and lecithin (Casey, 1979; Davis et al., 1979) [see Janowsky et al. (1994) for review]. Importantly, symptoms observed after administration of these compounds were similar to those that manifest in naturally occurring depression (Janowsky et al., 1994). These depressive states induced by cholinergic agonists or acetylcholinesterase inhibitors were observed in a wide range of populations, including healthy subjects (Risch et al., 1981; Nurnberger et al., 1983), marijuana-intoxicated subjects (El-Yousef et al., 1973), patients with Alzheimer's (Davis et al., 1979), and patients with a psychiatric illness such as depression, schizophrenia, or bipolar disorder (Janowsky et al., 1974, 1980). Furthermore, patients with an affective component displayed an exaggerated depressive behavioral response after increasing central acetylcholine levels compared to healthy volunteers. Hence, a super- or hypersensitivity of patients with endogenous depression or bipolar disorder for cholinergic manipulations was observed, supportive of a cholinergic imbalance during periods of depression (Janowsky et al., 1994).

In further support of the central acetylcholine-mediation of effects, the centrally acting agent physostigmine antagonizes mania and induces depression, whereas its non-centrally acting congener neostigmine does not, thus suggesting a central mechanism (Janowsky et al., 1973b). In addition, the centrally acting muscarinic antagonist scopolamine blocks the effects of physostigmine, whereas the non-centrally acting methscopolamine does not cause behavioral effects (Janowsky et al., 1986). Further supporting a role for central muscarinic acetylcholine mechanisms in contributing to depression comes from neuroendocrine and sleep electroencephalography (EEG) studies. Physostigmine administration increases serum adrenocorticotropic hormone, cortisol, epinephrine, and β-endorphine serum levels, all neuroendocrine compounds that are increased in endogenous depression (Janowsky et al., 1986) and concomitantly increase pulse and blood pressure levels. Furthermore, physostigmine further shortens the sleep EEG marker rapid eye movement (REM) latency in depressed patients. REM latency shortening itself is thought to be a marker of depression, an acetylcholine-mediated phenomenon that increases blood pressure and pulse rate (Dube et al., 1985; Sitaram et al., 1987). Significantly, these physostigmine-induced changes, as with the behavioral, cardiovascular, and neuroendocrine changes described above, are antagonized by scopolamine (Janowsky et al., 1986). Hence, centrally acting acetylcholine, acting particularly via muscarinic acetylcholine receptors, mediates physiological changes similar to those present during depressive behaviors.

Importantly, investigations into the mechanisms underlying depression and mania support an adrenergic–cholinergic balance. Intravenous administration of the dopamine/norepinephrine reuptake inhibitor methylphenidate antagonized the depressive behavior induced by physostigmine in humans (Janowsky et al., 1973a). Conversely, the behavioral activation and manic symptoms caused by methylphenidate were antagonized by physostigmine (Janowsky et al., 1973a), supporting an adrenergic–cholinergic balance hypothesis. Moreover, methylphenidate as well as other psychostimulants such as amphetamine can induce symptoms relevant to mania in healthy persons (Peet and Peters, 1995) or exacerbate symptoms of mania in patients with bipolar disorder (Meyendorff et al., 1985; Hasler et al., 2006). Therefore, mania was thought to involve an underlying pathophysiology of hypocholinergia and increased adrenergic signaling in contrast to depression, which was thought to have the converse.

Since the original concept of the adrenergic–cholinergic hypothesis was proposed in 1972 and the latest review was written in 1994, years of extensive research have been conducted. Both preclinical and clinical studies have led to significant discoveries, warranting an updated review on this potential neurochemical imbalance theory underlying bipolar disorder. Today's technology is far superior to that available a few decades ago, with neuroimaging techniques such as magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) including novel radioligands being possible to quantify receptors in vivo in the human brain. Other techniques include different manipulations such as viral knockdown of genes in animal models. At the time of the adrenergic–cholinergic hypothesis of bipolar disorder, little was known about dopamine, let alone its contribution to mania. More recently however, research supports a strong contribution of dopamine to the mechanism(s) underlying mania. Hence, a catecholaminergic (i.e., dopamine and norepinephrine) mechanism may better describe the potential biological underpinnings of mania. Although the importance of the cholinergic system during depression was recently reviewed (Dagyte et al., 2011), bipolar disorder was not its primary focus and it was not contrasted with mania. Thus, the purpose of this comprehensive review is to provide an overview of recent evidence from both human and animal studies that support a catecholaminergic–cholinergic balance theory of bipolar disorder.

The original adrenergic–cholinergic balance hypothesis of mania and depression in bipolar disorder is updated with recent observations in a revised catecholaminergic–cholinergic hypothesis of bipolar disorder. First, we discuss clinical findings regarding the involvement of the cholinergic and catecholaminergic system and their interactions in bipolar depression and mania respectively. We summarize data from neuroimaging studies, discuss neuropharmacological evidence, and briefly mention some genetic association studies. While discussing depression, it is important to note that it currently remains difficult to differentiate between bipolar and unipolar depression. We have therefore included findings from both affective states, highlighting differences and interactions where they occur. After a clinical update, we will discuss observations from preclinical studies investigating both the cholinergic and catecholaminergic systems in animal models. Finally, recommendations for future studies are made followed by concluding remarks.

2.1. Bipolar depression—evidence from humans

The original hypothesis of bipolar disorder was largely based on findings of increased acetylcholine by different manipulations causing depression. Since then, a variety of studies have supported these observations and renewed interest in this old theory. Studies have also led to a monoamine deficiency theory, in particular reduced serotonin deduced from the efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression. Here, we will update evidence regarding the involvement of the cholinergic system in depression (Table 1).

2.1.1. Observations from neuroimaging studies

In order to present an overview of neuroimaging data concerning cholinergic receptors, it must be mentioned that over the past