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Black bile: Are elevated monoamines an etiological factor in some cases of major depression?

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ABSTRACT

It was hypothesized decades ago that reduced levels of brain monoamines such as serotonin or norepinephrine form, at least in part, a pathophysiological basis for major depression. Consistent with this hypothesis, a conventional strategy used, with varying success, to treat major depression involves administering antidepressant drugs that are thought to boost the synaptic concentration of serotonin and/or norepinephrine. While the reduced monoamine hypothesis is well known but highly controversial and widely considered to be incomplete or simply incorrect, the possibility that elevated monoamines are an etiological factor in some cases of major depression (rather than or in addition to hypomania or mania) has received little attention at all. This paper puts forth the novel hypothesis elevated brain levels of three monoamines – serotonin, norepinephrine, dopamine – are each etiological factors in some cases of major depression. In support of this hypothesis, the paper very briefly reviews relevant data on each of these neurotransmitter systems, including: transporter knockout mice, human genetic association studies, and pharmaceutical studies that enhance or diminish transmitter signaling in either rodents or humans. While all of the published data do not support the hypothesis, there are studies that do for each of the three transmitter systems. The etiological basis of the putative effect of monoamines on depression may be mediated both through genetics and exposure to psychological stress. If the elevated monoamine hypothesis is correct for some persons, pharmaceutical treatment of depression may be significantly improved if the particular elevated monoamine(s) could be identified and then altered on a personalized basis, or perhaps for different putative subtypes of depression. One possibility is that atypical depression involves elevated noradrenergic signaling.

Introduction

It was hypothesized in the 1960s, which were groundbreaking years for pharmacological treatments in psychiatry, that reduction in brain monoamine levels may in part form a pathophysiological basis for at least some cases of major depression; e.g., the theories of Schildkraut and Coppen [1,2]. These theories were supported by the observation that newly created antidepressant drugs, including tricyclics and monoamine oxidase inhibitors, boosted the synaptic monoamines serotonin (5-hydroxytryptamine; 5-HT), norepinephrine (NE), and dopamine (DA; for the latter category of drugs) [3]. These two categories of antidepressant drugs, along with the more recently created selective serotonin reuptake inhibitors (SSRIs; such as fluoxetine) and serotonin norepinephrine reuptake inhibitors (SNRIs; such as duloxetine), remain principal pharmacological treatments for major depression to this day [4], further supporting the hypothesis. Schildkraut (1965) [1] also suggested that elevated levels of catecholamines (i.e., NE and DA) may form a basis for mania, rather than depression. Janowsky et al. (1972) [5] later expanded upon this idea, suggesting that a high ratio of NE to acetylcholine (another neurotransmitter) results in mania, whereas a low ratio results in depression. Consistent with these hypotheses, a study that included two persons with rapidly cycling bipolar disorder found that the blood plasma concentration of the NE metabolite, MHPG, was significantly higher during mania than during depression [6].

While there is theoretical and empirical support for the hypothesis decreased brain levels of monoamines produce depression and increased levels produce mania, this notion is widely regarded as incomplete or as even simply wrong [7]. For example, a number of clinical studies have failed to find significantly lower levels of 5-HT or NE metabolites in cerebrospinal fluid (CSF), plasma, or urine in depressed persons relative to healthy controls; e.g., references [8,9]. Furthermore, other studies have suggested that monoamine boosting antidepressants (and perhaps all conventional antidepressants) are either no better than placebo at treating depression, or are only slightly better [10]. While these various contrary findings do not rule out the reduced monoamine hypothesis, they may suggest that reductions in synaptic monoamines do not form the basis of all cases of major depression.

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Hypothesis: elevated monoamines are an etiological factor in some cases of major depression

This paper puts forth the hypothesis elevated brain levels of monoamines, specifically 5-HT, NE, and DA, are an etiological factor in some cases of major depression. This is, to my knowledge, a novel hypothesis, referred to subsequently as the elevated monoamine-depression (EMD) hypothesis. This hypothesis suggests these three monoamines contribute independently to causing and/or worsening depression, and further that they each have "operating ranges" whereby too high or too low a synaptic concentration is pathological with regard to depression, which may complement the reduced monoamine hypothesis described above. Elevated monoaminergic transmission may be the result of genetics and/or psychological stress, since the latter can result in enhanced release of monoamines [11], which is most often associated with increased NE release. A more general variant of the EMD hypothesis is elevated synaptic transmission of these monoamines, whether caused by increased synaptic concentration or increased sensitivity of their postsynaptic receptor populations, is an etiological factor in some cases of depression.

Published data relevant to the hypothesis

Published studies relevant to the EMD hypothesis are very briefly reviewed below. This is certainly not meant to be an exhaustive survey of these data, but rather to present some representative studies that largely support the hypothesis. Lines of evidence include: transporter knockout mice, human genetic association studies, pharmaceutical studies that enhance or diminish transmitter signaling in either rodents or humans, and association of psychological stress with depression or depression-like behavior.

Elevated serotonin and depression

5-HT transporter knockout mice, which have elevated synaptic 5-HT [12], can exhibit depression-like behavior (i.e., increased immobility) in the forced swim test (FST) [13]. Moreover, mice chronically treated with the 5-HT boosting drug fluoxetine also exhibited increased immobility in the FST [14]. However, a rat study found that subchronic administration of 5-HT boosting antidepressants such as fluoxetine decreased FST immobility by increasing swimming, whereas NE boosting antidepressants such as desipramine decreased immobility by increasing climbing [15].

The short allele of the 5-HT transporter-linked polymorphic region gene, which may lead to greater synaptic 5-HT, is associated with both subsyndromal depression [16] and major depression [17]. The antidepressant tianeptine may achieve its therapeutic effects by lowering synaptic 5-HT [18].

Elevated norepinephrine and depression

The NE release-lowering drug clonidine potentiated the effects of various antidepressants in the mouse FST [19]. In a behavioral despair rat model of depression, immobility induced by the acetylcholine boosting drug physostigmine was blocked by pretreatment with the noradrenergic beta receptor blocker metoprolol, and partially blocked by clonidine [20]. However, NE transporter knockout mice, which may have elevated levels of synaptic NE, exhibited the antidepressant-like effect of decreased immobility in the FST and tail suspension test (TST) [21].

While noradrenergic transmission reducing beta blockers, such as propranolol, have been reported to increase risk for depression, a statistically non-significant *decrease* in risk has also been reported [22]. It has been argued that since some antidepressants may act by reducing the sensitivity of postsynaptic beta adrenoceptors, the pathophysiology of depression may involve increased noradrenergic transmission [23].

A clinical study showed that atypical depression responds better to the 5-HT boosting drug fluoxetine than it does to the NE boosting drug nortriptyline [24], possibly consistent with the notion that the etiology of atypical depression involves elevated NE. Consistent with this view, a study that measured cortisol responses to challenge with the NE boosting antidepressant desipramine, found evidence for a less impaired NE system in persons with atypical depression compared with that in other depressed persons [25].

There is evidence for elevated levels of corticotropin-releasing factor in endocrine circuits during major depression, and through excitatory input to the locus coeruleus this could lead to elevated brain NE in depression [26]. A study found that although plasma NE is frequently elevated in essential hypertension, persons with endogenous depression had higher plasma NE concentrations but lower blood pressure than persons with essential hypertension [27].

Elevated dopamine and depression

A meta-analysis of antidepressant augmentation with atypical antipsychotics, which block DA signaling, in treatment resistant depression found a significant potentiation of effect [28]. The Met variant of the catechol-O-methyl transferase (COMT) Val(158)Met polymorphism may produce greater synaptic DA and is associated with depression in humans [29]. Elevated DA signaling is associated with schizophrenia, whose negative signs resemble depression, and actual depression is frequently comorbid with this disorder [30]. However, DA transporter knockout mice, which may have increased levels of synaptic DA, showed decreased immobility in the FST and TST [21].

A point potentially related to all three monoamines: the monoaminergic transmission reducing drug reserpine has been associated with antidepressant effects in humans [31]. Also, the antidepressant properties of S-Adenosyl methionine (SAM-e) [32], a molecule that helps metabolize catecholamines, may provide additional evidence for elevated catecholaminergic transmission in major depression.

Evaluation of the elevated monoamine-depression hypothesis

The above data are consistent with the preliminary hypothesis that elevated monoamines play an etiological role in some cases of major depression, and this could be investigated further in human subjects and rodent models through administration of monoaminergic-transmission reducing drugs.

One question in evaluating the EMD hypothesis is whether putatively elevated monoamines are mainly the result of genetics such as transporter-linked polymorphisms [16,17] or instead of psychological stress? Major depression can be associated with exposure to marked psychological stress, such as trauma [33]. Since psychological stress is associated with elevated release of brain monoamines in rodents [11], perhaps significant or prolonged stress could produce chronically elevated monoamines in humans, resulting in major depression. Alternatively, marked release of brain monoamines due to psychological stress might subsequently result in a depletion of their synaptic level, which could also result in major depression.

In assessing the EMD hypothesis by comparing CSF, plasma, or urine levels of monoamines or their metabolites in persons with or without major depression, perhaps neither diminished nor