Review Article

Molecular Mechanism of Depression: A narrative review of the leading neurobiological theories of Depression

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Abstract

Affective disorders, notably major depression and anxiety, are a significant cause of mortality and morbidity in society today, with the prevalence of depression estimated to be 10-16% in the general population and it is important to have effective treatments available for potentially life-threatening affective disorders. Yet, our understanding of the pathophysiology of depression and anxiety disorders has traditionally been limited due to the difficulty in investigating the brain *in vivo*. Thus, the molecular bases of these medication targets remain unclear. Recent advances in neuroscience have allowed us to gain a better understanding of the pharmacological basis of medical treatments for affective disorders. This new knowledge may pave the way for improved management of depression and anxiety. This review summarises some of the leading theories surrounding the neurobiology of depression and link them with both current and potential pharmacological treatments for depression

Introduction

Mood disorders, including chronic anxiety states and major depressive disorder (MDD) are colloquially referred to as depression. MDD is primarily defined by such features as significantly low mood throughout most of the day and/or the loss of interest or pleasure in previously enjoyable activities, persisting for a period of at least two weeks [1]. It is a psychiatric condition with a serious risk of suicide. Worldwide, depression is becoming a significant burden with respect to global health. The World Mental Health Survey Initiative conducted by the World Health Organization found lifetime prevalence of anxiety disorders to be between 9.9% and 16.7% and that of depression to be between 9.8% and 15.8% [2]. Locally, the results of the 2012 Australian Health Survey indicated that 2.1 million Australians, or 9.7% of the population, currently experience a mood disorder and that over 800,000 Australians, or 3.8% of the population, report having an anxiety disorder [3]. Together, anxiety and depression have the highest reported prevalence of any mental illness in the Australian population [3]. Since the efficacy of existing treatments for MDD have been called into question, there is a pressing global need for safe and effective treatments [4,5]. This article intends to review major theories about the biological basis of MDD in relation to the mechanism of action of therapeutic substances. Beyond biomedical models, there are also psychological models that may play a part in the development of MDD such as cognitive and psychodynamic theories, which will not be covered in this review.

Monoamine Hypothesis

The first generation of antidepressants include monoamine oxidase inhibitors (MAO-I) and tricyclic antidepressants (TCA). MAO-Is block the breakdown of neurotransmitters such as dopamine (DA), noradrenaline (NA), serotonin (5HT), while TCAs block the reuptake of these substances back into the cells. These mechanistic insights in the 1960s led to the proposition of the monoamine hypothesis of depression, which posited that a functional deficiency in at least one of the three biogenic monoamine neurotransmitters may be implicated in depression [6]. Clusters of neurons producing these neurotransmitters have been localised in various regions of the midbrain, hypothalamus and pons, with projections to the thalamus and higher cortical areas [7]. While 5HT was the first substance implicated as a 'depression' neurotransmitter, the other monoamines may be involved in modulating the symptomatology of depression, perhaps giving rise to different biological 'subtypes' of depression [7–9]. Quite likely, these key neurotransmitters work in an integrated fashion, despite having distinct biochemical and neuroanatomical pathways. For example, in experimental animals studies, the combination of a NA reuptake inhibitor with a 5HT and NA receptor antagonist enhanced release of DA within the prefrontal cortex, whereas the individual drugs had a lesser effect [10]. This suggests a considerable degree of interaction between NA, DA and 5HT.

Clinical Applications

The monoamine hypothesis of depression remains one of most enduring explanations for the development of depression. Indeed, it is the explanation provided to patients beginning antidepressant agents such as selective serotonin reuptake inhibitors (SSRI), although the uncritical manner, in which this is described to the general public has been criticised [11]. Nonetheless, most anti-depressive medications, currently in the market, implicitly lend credence to the monoamine hypothesis, in that their net effect is to increase intrasynaptic concentrations of DA, NA or 5HT with the assumption that at least one of these substrates is deficient. Evidence of the endurance of the monoamine hypothesis can also be inferred from

more recent studies which overall intend to extend its validity and will be evaluated in this article. While several alternative models are described below, the putative role of neurotrophins in MDD is in particular linked directly to the monoamine hypothesis, since these substances must act upon monoamine neurotransmitters to exert their beneficial effects [12].

Critical Analysis of the Theory

As noted above, the efficacy of mainstream antidepressants has been repeatedly criticised during the past two decades. Some authors have argued that the antidepressant effects of SSRIs (i.e. Prozac), can be attributed solely to placebo effects [13–15]. However, other research has shown the opposite, that SSRIs indeed impart some clinical benefit [16]. The conflict revolves around the interpretation of effect sizes using arbitrary interpretations of effect size [15–18]. Effect size interpretations need to be considered in a particular clinical context [18]. Regarding SSRIs and other antidepressants, effect sizes must be interpreted in the context of other available psychiatric treatments. Psychotherapeutic approaches to the treatment of depression are an example of a non-pharmacological alternative; however, the effect size for such approaches may be considerably smaller than medication-based approaches, with Cohen's d of just 0.22 [19]. Like psychopharmacological research, psychotherapeutic research is subject to significant publication bias, resulting in distortion of the reported data [19,20]. In addition, the effect sizes of psychoactive medication are comparable to other pharmacological treatments for a number different medical conditions [21].

Taken together, these studies suggest that whilst medication is not a definitive treatment for MDD, it is effective in alleviating symptoms across a broad section of the clinically depressed population. The effect size of 0.32 in studies comparing the effectiveness of antidepressants to psychotherapy provides support for antidepressants being the best current treatment for depression [16]. The effect sizes correspondingly suggest the monoamine hypothesis does not account entirely for the phenomenon of MDD. The known 2 to 3 weeks delay from the initial administration of current antidepressant medications to observed efficacy also supports this proposition, in that some additional factors must come into play [22]. These may include downstream gene expression changes caused by chronic treatment with antidepressants. Thus, targeting monoamines may not directly target the core mechanisms underlying MDD, or indeed anxiety disorders. It is now speculated that SSRIs and other contemporary antidepressants must be acting upon additional pathways to bring about the observed treatment efficacy [22].

In clinical practice, there are other issues related to the efficacy of antidepressants. They must often be taken over long periods of time, possibly for years, to protect patients from relapse. In addition, the major side effects associated with antidepressants, such as weight gain, insomnia and sexual dysfunction, can be disruptive to daily living. This contributes to poor compliance rates in patients, which in turn increases the likelihood of relapse [22].

The monoamine hypothesis of depression has resulted in a search for evidence of the presumed monoamine substrate deficiency in patients diagnosed with MDD. This research has been facilitated in recent years by molecular imaging with positron emission tomography (PET) and other methods employing tracers for the 5HT transporters. A meta-analysis of 20 such publications demonstrated a reduction in 5HT transporter levels in untreated MDD patients with an effect size of approximately 0.5 [23]. However, the meta-analysis showed that there was only a 10% difference in the number of 5HT transporters between patients with

depression and normal controls. This suggests that serotonin on its own may not fully account for this disorder. These substantive issues have led researchers to explore other potential avenues to explain the neurobiology of depression. To date, newer theories of depression have not supplanted the monoamine hypothesis, but rather complement the monoamine hypothesis in exploring the fundamental causes of depression.

Brain-Derived Neurotrophic Factor

Current neurobiological explanations of depression consider the intracellular response of neurons to monoamines, in an extension of the existing monoamine hypothesis of depression. When neurotransmitters such as NA, DA, or 5HT bind to their receptors, they activate a variety of second messengers within the post-synaptic neuron. An important target protein in this process is cAMP response element-binding protein (CREB), which begins the gene transcription process and regulates the production of mRNA. One of the genes that is regulated through the CREB pathway encodes a brain-derived neurotrophic factor (BDNF) – a protein responsible for the development of new neurons as well as the growth, differentiation and interconnections formed between existing neurons [12]
Chronic stress reduces the expression of BDNF in the hippocampus [12,22,24]. This reduced expression may be mediated in part through epigenetic means, providing a potential explanation of how environmental factors can induce depressive symptoms that persist past the period of actual stress [24]. Serum taken from patients with depression show lower BDNF levels compared with non-depressed subjects and the chronicity of the depression was linked with an increase in BDNF levels [25]. In both human and animal studies, antidepressant treatment with SSRIs and Serotonin/Noradrenaline Reuptake Inhibitors appears to increase BDNF levels and reduce depressive symptoms [22,26,27]. This exciting development means that BDNF, as well as its target receptor TrkB, are targets for potential new treatments for depression, but, no clinical trials have been performed on new medications of this class at the time of writing [28].

Clinical Applications

Electroconvulsive therapy (ECT) is the application of electrical current to patients with the aim of inducing an epileptic event. Controlled seizures can bring rapid remission of depressive symptoms [29]. First used in the late 1930s, ECT's mechanism of action has long been a mystery, but recent research suggests that an epileptic event increases BDNF levels within the hippocampus [30]. This is supported by animal studies showing that increases in BDNF levels and reduction of depressive-type symptoms occur following electrical stimulus of pre-limbic areas of the brain [26]. Indeed, BDNF serum levels at pre-treatment baseline can predict whether or not a patient will respond to ECT [31]. Emerging treatments for depression, such as transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS) may also operate through increasing BDNF levels [32,33].

Neuropeptides

Investigation into the potential involvement of hypothalamic neuropeptides in a monoamine hypothesis of depression represents a more recent approach to investigating MDD. The potential therapeutic use of oxytocin analogues and vasopressin antagonists has received increasing attention in the past few years. The theoretical justification for this new focus involves the interactions between oxytocin and 5HT systems, as well as vasopressin and the classical hypothalamic-pituitary-adrenal (HPA) axis, long implicated in depression, anxiety, and stress-related disorders.

Oxytocin

Oxytocin is a neurohormone produced primarily in the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus and is then secreted from the posterior pituitary gland [34]. Its traditional physiological role involves the promotion of uterine contractions during parturition as well as triggering lactation soon after birth to allow the release of breast milk [35,36]. Recently, oxytocin has been found to be involved in signalling other behavioural and physiological processes, including maternal bonding, social behaviour, self-perception, sexual behaviour and pair bonding [37–39].

More recent studies investigate oxytocin's potential involvement in mood disorders, a line of research that has been substantiated by the growing evidence of the links between oxytocinergic and 5HT systems [40]. Anatomical evidence suggests that serotonergic projections from the DRN and MRN have substantial connections with the anterior magnocellular region of the PVN and anterodorsal parts of the SON, where there are large numbers of oxytocinergic cells [41,42]. In addition, some effects of the SSRIs are known to be mediated in part through oxytocinergic neurons and the hypothalamus has a very dense serotonin innervation [43].

Further support for the role of oxytocin in depression arises from the observation that plasma oxytocin levels appear to be affected by early childhood stress, a risk factor for depression in later life [44]. A reduction of plasma oxytocin in people with low-high levels of depressive symptoms, has been seen in humans [45,46]. Caution must be taken in interpreting these studies, as plasma oxytocin is unlikely to be representative of central oxytocin release; oxytocin does not readily cross the blood-brain barrier [47]. Nonetheless, these findings compliment earlier studies, which have shown that oxytocin inhibits the HPA axis activity in animal models of stress [38]. Indeed, the first investigations of the antidepressant effects of oxytocin were carried out in Sprague Dawley rats [48]. In this study, administration of the oxytocin analogue carbetocin reduced immobility of the rats in the Forced Swim test. Immobility, a sign of behavioural despair, is often used as a proxy to measure depressive-type behaviour in animals [49]. This result suggests that oxytocin has a role in alleviating depressive-type disorders in humans. A similar finding was found using the elevated plus maze, which is a test for anxiety-type behaviours in animals [50]. However, generalisation of those studies is limited since they did not use a validated model of acquired depression.

Many of the proposed mechanisms for the effects described above involve interactions between oxytocin and other neuronal systems. One recent explanation proposes that the connections between 5HT neurons of the raphe nuclei to the PVN of the hypothalamus via the medial forebrain bundle can trigger oxytocin release in the hypothalamus. This may in turn reduce release of corticotrophin releasing factor (CRF), a key hypothalamic hormone of the HPA axis, which is involved in both depression and anxiety aetiology [38,51]. Another model focuses on the role of second messengers triggered when oxytocin binds with its receptors, causing changes to expression of CREB and downstream effects on BDNF [34]. It is possible that the combination of CRF and second messengers together bring about the mood and behavioural changes associated with depression and anxiety, but further work is required to understand the precise molecular mechanisms involved as well as the interaction of these systems with the environmental and psychological stressors that can give rise to depression and anxiety.

Overall, this line of evidence demonstrates the integral nature of oxytocin in relation to its involvement in both depression and anxiety. Oxytocin in many ways serves as a bridge,

linking previously known functions of other monoamine neurotransmitters in relation to existing neurobiological theories of depression and thus potentially extending our understanding of the mechanisms underlying depression and anxiety. Certainly there is a need for further research to resolve the many limitations that still prevent the conclusive demonstration of a link between oxytocin and depression.

Critical Analysis of the Theory

A meta-analysis has suggested that intranasal oxytocin may be effective in the management of depression [52]. This effect may also be additive with current antidepressant medications, but these studies have been criticised for their methodology, with critics suggesting that it is physiologically impossible for therapeutic levels of oxytocin to enter the brain via the intranasal route [53]. Further, many of the outcome measures used in these studies, such as serum oxytocin, have been shown to not correlate with levels of central oxytocin [47,54].

Given that oxytocin has physiological functions in uterine contractions as well as central actions, there has been significant research connecting post-partum depression (PPD) and oxytocin levels. Patients in third-trimester pregnancy that had lower expression of oxytocin receptor (OXTR) genes in cortical tissue, and lower plasma levels of oxytocin were more likely to develop PPD [55,56]. Interestingly, childhood abuse appears to have a potentiating effect on OXTR gene expression, which supports other studies that found epigenetic changes between maternal stress and OXTR expression [55,57]. Of note, many of these studies have utilised genome-wide associations with small sample sizes, which may be underpowered [17,58,59].

As implied by the low effect size in many antidepressant trials, many patients are unresponsive to conventional treatments, which is termed treatment-resistant depression. Patients with treatment-resistant depression in one study were shown to have high serum levels of oxytocin compared to non-depressed controls [60]. Patients with treatment-responsive depression had lower plasma levels of oxytocin compared to the treatment-resistant patients, suggesting that oxytocin may discriminate between these types of depression, but the small sample size again calls for caution in interpretation of these results. Of treatment-resistant group, four out of ten patients had serum oxytocin levels different from the rest of the group, whilst the other six patients had similar serum levels to both the treatment-resistant depression group and control group. This raises the possibility that the differences found was due to outliers in the data, rather than representing significant differences. Similar to the criticisms levelled at studies looking at intranasal oxytocin, it is questionable whether serum oxytocin levels correlate with levels of oxytocin in the CNS, particularly before treatment with oxytocin [47,54].

Since other human studies have suggested that low levels of oxytocin may be associated with depressive symptoms, this issue can only be resolved in sufficiently powered clinical studies [56].

Conclusions

Decades after the emergence of the monoamine model of depression, defining the pathophysiology of mood disorders remain an elusive goal. Existing antidepressants are moderately effective at treating depression, but they have significant side effects limiting their use. In addition, some patients are non-responders to these medications. This has spurred further research into other mechanisms involved in the pathophysiology of mood disorders that extend beyond the classical monoamine-based theories, but these new theories do not supplant previous ideas, rather compliment them. To date, these recent developments have not yet been translated into new pharmacological treatments for mood disorders. Nonetheless, the inclusion of factors such as BDNF and neuropeptides in our understanding of the pathophysiology of depression allow a greater understanding of how existing treatments may work at a molecular level. Future research should aim to further elucidate these new theories and provide further stimulation for medication and/or procedural development.

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