Are Antidepressants Mood Agents Or Anxiolytic Drugs?

Michel Bourin*

Neurobiology of anxiety and mood disorders, University of Nantes, France

Received: May 23, 2018; Accepted: June 29, 2018; Published: July 05, 2018

*Corresponding author: Michel Bourin, Neurobiology of anxiety and mood disorders, University of Nantes, France, Email: Michel.bourin@univ-nantes.fr

Abstract

Many advances have been made in the treatment of depression with the recent discovery of selective serotonin reuptake inhibitors (SSRIs) and mixed serotonin and norepinephrine reuptake inhibitors (SNRIs). Behavioral, electrophysiology, and microdialysis studies have shown that serotonin receptors, mainly the 5-HT1A, 5-HT1B, and 5-HT2C subtypes, play a key role in modulating antidepressant activity. The indirect activation of serotonergic receptors by antidepressants could lead, via an increase in 5-HT concentrations in the synapse of certain brain regions, to the activation of G proteins which would cascade the transcription of neurotrophic factor such as "the brain-derived neurotrophic factor" (BDNF). Depression could be considered as an anomaly of transduction mechanisms, this hypothesis needs to be deepened by molecular biology studies.

The fact that antidepressants are also active in the treatment of anxiety disorders, questions about the nature of their mechanism in these various pathologies.

Key words: Antidepressants; Serotonin Receptors; Mood Disorders; Anxiety Disorder

Introduction

Although several hypotheses have been put forward, the aetiology of depression is still poorly defined. The first major theory of depression, i.e., the monoaminergic theory, proposes that this disorder is due in particular to a deficiency of serotonin (5-HT) and norepinephrine (NA) [1, 2, 3, and 4]. Moreover, some molecules that deplete these neurotransmitters, such as reserpine, can induce a depressive state in a small percentage of individuals. However, this simplistic theory cannot explain the pathophysiology of depression by itself since the efficacy of antidepressants is observed clinically after a few weeks of treatment. A second hypothesis based on neurotransmitter receptors has been issued. According to this hypothesis, the depression is due to an abnormal functioning of the monoamine receptors. This receptor disruption could itself be caused by depletion of monoaminergic neurotransmitters. Advances in molecular and cellular biology suggest the role of neurotrophic factors, such as the "brain-derived neurotrophic factor" (BDNF) suggesting a neurodegenerative hypothesis to the pathophysiology of depression [4, 5].

In addition, antidepressants are now widely used in the treatment of anxiety disorders, whether generalized anxiety, panic disorder, social anxiety and post-traumatic stress, which makes it possible to wonder about the different nature of their mechanism of action.

Targets for action of antidepressants

Serotonergic receptors

Role of 5-HT1A receptors on antidepressant activity

Various behavioral, electrophysiological and microdialysis studies have highlighted the role of 5-HT1A receptors in the pharmacological properties of antidepressants. Thus, the effects of the administration of a single dose of antidepressant on an animal model of desperation (forced swimming test) carried out in mice, suggests that the action of imipramine is via the 5-HT1A postsynaptic receptors [6]. Blier and de Montigny [7] in electrophysiology studies have shown that chronic treatment with a selective serotonin reuptake inhibitor (SSRI) induces functional desensitization of 5-HT1A autoreceptors in nuclei of the dorsal raphe. Moreover, although no down-regulation of 5-HT1A autoreceptors in dorsal raphe nuclei has been observed in binding studies [8], microdialysis studies have been conducted [9, 10], have shown that chronic treatment with SSRIs causes hypofunction of 5-HT1A autoreceptors. In contrast, postsynaptic 5-HT1A receptors do not react in the same way as 5-HT1A autoreceptors to chronic treatment with SSRIs. Indeed, postsynaptic 5-HT1A receptors, located in the hippocampus, do not undergo desensitization or "down regulation".

The 5-HT1A autoreceptors appear to be a brake on the rapidity of action of antidepressants. Indeed, during the first days of treatment the excess of NA and especially 5-HT intrasynaptic will activate autoreceivers [11]. This phenomenon called negative feedback will slow the system back. Also, a more current research pathway tries to induce in the same molecule properties that would increase the speed of action of antidepressants, this would be the case of the blocking of presynaptic 5-HT1A receptors by the (-) pindolol (molecule having antagonistic properties at alpha-adrenergic receptors, 5-HT1A and 5-HT1B). Indeed, clinical studies show that the co-administration of (-) pindolol with an IRSS (flumazenil or paroxetine) would induce a faster mood improvement in depressed patients [12-16]. This hypothesis remains controversial and is the subject of lively debate [17-19].

Role of 5-HT1B receptors on antidepressant activity

Pre-clinical studies have shown that serotonin reuptake inhibitors appear to act indirectly on 5-HT1B receptors [8]. This
Antidepressants do not only act by inhibiting monoamine reuptake, but also affect neurotransmitter receptors. This stimulation of the receptors causes the activation of transcription factors present inside the nucleus of the cell, via the G proteins. This activation of the transcription factors decreases the synthesis of the receptors: it is the "down regulation". These successive activations stimulate the release of a trophic factor - BDNF. Does this stimulation account for the increased size of the hippocampus mentioned above, which is a consequence of the action of antidepressants? This is related to the important notion that antidepressants would not only act on neuromodulators but also on neuronal growth factors [1, 5]. Nibuya et al [35] showed in the rat that chronic administration of antidepressants [desipramine, imipramine, fluoxetine, sertraline] increased the BDNF concentration and the corresponding trkB receptor mRNA expression. The expression "cAMP response element binding protein" [CREB] is also increased in the hippocampus. These results would indicate that the administration of an antidepressant, by increasing CREB synthesis, would regulate certain genes such as that encoding BDNF and its trkB receptor. Recently, other pre-clinical studies have confirmed this hypothesis. Thus, Martin et al [36] showed that the amount of BDNF mRNA was increased after chronic treatment with an antidepressant. Vollmay et al. [37] in an animal model of depression, the rat-acquired resignation test, show that chronic treatment with antidepressants or with...
seismic therapy prevents the reduction of stress-induced BDNF expression. BDNF would exert its neuronal protective action by autocrine activity on hippocampal neurons and paracrine activity on the neurons that innervate this region. The autocrine activity is very important in depressions associated with severe chronic stress, in which there is a decrease in the concentration of BDNF, leading to atrophy of the hippocampus and, in the worst case, to a reduction in the number of hippocampal neurons [38]. Paracrine activity of BDNF may increase the functions of neurons [serotonergic and noradrenergic] innervating the hippocampus. Indeed, Sklair-Tavron and Nestler [39] have shown that BDNF increases the survival and growth of hippocampal neurons. Animal studies have shown that imipramine antidepressants and their derivatives can behave as compounds that interact with G proteins [40]. Thus, it is plausible to hypothesize that depression could be considered a disorder of the super family of G-proteins coupled to a receptor. This disorder, determined by a genetic defect in some cases, could be expressed at the level of the receptor or alternatively in the G proteins thus leading to a faulty coupling between the receptor and the G protein and thus leading to abnormal transduction mechanisms. This hypothesis is to be studied mainly because the 5-HT1A receptors do not react in the same way to a chronic treatment of antidepressant according to their localization. Indeed, presynaptic 5-HT1A receptors are desensitized after chronic antidepressant treatment, whereas postsynaptic 5-HT1A receptors are not desensitized. The receiver, whatever its location, is nevertheless coded by one and the same gene. Therefore, the differences in antidepressant response would not be due to the receptor protein itself. It is possible that the presynaptic 5-HT1A receptor is coupled to a different G protein [Gi, GB] from that to which the postsynaptic 5-HT1A receptor is coupled. This suggests that the nature of G-protein coupled to the 5-HT1A receptor might be different from one brain region [dorsal raphe nucleus] to another [frontal cortex, ventral hippocampus]. The use of molecular biology and cell cultures, for example, should shed light on this issue. The pathophysiology of depression should be better studied anyway. What molecular perturbations [receptors, protein G, BDNF and other transcription factors] does it cause? A good experimental model remains to be defined and identified by Knock-Out or transgenic mice.

**Therapeutic problems related to antidepressant treatment**

**Are there more specific targets for antidepressants?**

At the end of the 1970s, the decrease in the number or sensitivity of beta-adrenergic receptors in the brain appeared to be implicated in antidepressant activity [41]. And since the clinical effect of antidepressants was felt after 15 days, it was thought that there was a rational explanation for antidepressant activity. This decrease also occurs in rats almost three weeks after the start of treatment. Unfortunately, at the moment there are antidepressants that do not lead to “down regulation” of beta receptors and that are clinically active in depression. This is particularly the case of the new antidepressants, that is to say the inhibitors of serotonin retreading. Although “down-regulation” of beta receptors is observed with fluvoxamine, fluoxetine and sertraline, it has not been observed for citalopram and paroxetine.

**The dose / effect relationship of antidepressants**

The existence of effect / dose relationships has long been lacking in psychiatry, depriving patients of significant potential benefits. Phase II drug development involves establishing this relationship but it was relatively erratic. With tricyclics in particular, a significant increase in the dose leads to inefficiency following a U-shaped effect / dose curve. Today, the proof of an effect / dose relationship has been established for two molecules: paroxetine and venlafaxine. Like paroxetine [42], venlafaxine is expected to have a low serotonin reuptake inhibitory dose and a norepinephrine reuptake inhibitor [43]. It is thus considered that starting at 150 mg and above, venlafaxine mainly inhibits the reuptake of norepinephrine [6]. Thus, for paroxetine, increasing...
the daily dosage from 20 to 40 mg / day significantly increases the proportion of responders. Although this dose increase is limited by the occurrence of side effects, the dose / effect relationship allows the patient to be offered a dose increase rather than an interruption of treatment and the change by another molecule. The establishment of a dose-response relationship for some antidepressants is a significant contribution to the treatment of depression.

**Inter-relationships between brain structures / neurotransmitters**

Knowledge of interrelationships between neurotransmission systems is very important. Activation or inhibition of one system is not without effect on others. For example, the noradrenergic and serotonergic system interacts with each other. Indeed, serotonergic cell bodies [present in raphe nuclei] and noradrenergic cell bodies [present in the region of the locus coeruleus] emit mutually projections from one to the other [Figure 1]. Thus, we find serotonergic heteroreceptors [5-HT2A] on the endings of noradrenergic neurons as well as noradrenergic heteroreceptors [alpha 1] on the cell bodies of serotonergic neurons. The alpha 2 noradrenergic receptor can itself be an autoreceptor or a heteroreceptor. Thus, activation of the alpha 2 noradrenergic autoreceptors of the locus coeruleus contributes to the reduction of the concentration of noradrenaline and serotonin in the frontal cortex via a decrease in excitatory noradrenergic fiber activity, mediated by postsynaptic alpha 1 noradrenergic receptors. Localized in the cell bodies of the neurons of the raphe nuclei. In addition, the activation of alpha 2 adrenergic autoreceptors present at the end of adrenergic neurons in the raphe nuclei may also inhibit the activity of serotonergic cell bodies [32].

**Evolution of the antidepressant concept**

The concept of antidepressant is evolving gradually since these molecules are used successfully to treat other mental pathologies than depression. Clomipramine was the first to prove an activity in the treatment of obsessive compulsive disorder [OCD] while other imipramines and derivatives are not effective. In fact, its desmethyl-clomipramine metabolite is a potent inhibitor of serotonin reuptake but also norepinephrine. The combined results of clomipramine and desmethylclomipramine on the inhibition of serotonin reuptake are much greater than those of other tricyclics. Other selective serotonin reuptake inhibitors, such as fluoxetine, fluvoxamine, sertraline and paroxetine, have also been shown to be effective in the treatment of OCD. Their effectiveness in treating this condition is clearly not related to their antidepressant properties as these drugs reduce obsessive-compulsive symptoms in patients who are not depressed.

As early as the 1960s, several studies have demonstrated the efficacy of MAOIs in anxio-phobic states, but the difficulty of using these derivatives has led them to use them only in severe cases or even to abandon them. These results have been confirmed more recently and new studies have been developed thanks to the use of potentially less toxic derivatives such as the MAO-specific inhibitors A. Liebowitz, in 1992 [49], took stock of the various controlled trials or not, versus placebo and concludes that these molecules have a particularly interesting efficacy in the treatment of social phobias.

It was Klein and Fink who first observed that imipramine was able to prevent panic attacks, later Klein [50] showed that imipramine was effective in the treatment of phobias with panic attacks but not effective in pure phobias. These observations led to the treatment of subjects with panic attacks with low doses of imipramine for preventive purposes, the high doses exaggerating the phenomenon. The dose is increased in steps until, after three months; doses of imipramine are similar to those usually used in depression.

Finally, in a recent study Rickels et al. [51] showed that imipramine and trazodone were effective in the treatment of generalized anxiety. Imipramine results in better results than trazodone and diazepam compared to placebo after 6 and 8 weeks.

This work confirms earlier work that had been conducted in patients with anxio-depressive pathology [52, 53]. Now the various IRS have received their marketing authorization in generalized anxiety and other anxiety disorders.

The fact that antidepressants are active in the treatment of anxiety disorders led us to seek the explanation of their mechanisms of action in these pathologies.

It turns out that the 5-HT2A receptors can participate in this activity. It seems more and more obvious that this action would be exerted at the amygdala, a cerebral structure that seems to be a “Filter” on the perception of emotions and which is rich in 5-HT2A receptors.

**Conclusion**

It is important to recall a now admitted fact that depression must be conceptualized as a recurrent illness that requires treatment at the time of the episode and in the long run to avoid relapse. Indeed, all antidepressants are effective in the acute phase of the disease and the prevention of relapses requires continuation of long-term treatment and the same dosage. Finally, the neurobiological bases of relapses and recurrences are, to date, unknown. Relapses and recurrences likely involve complex mechanisms of pre- and post-synaptic regulation. While considerable progress has been made recently, the treatment of depression needs to be further improved.

High hopes lie in the research that is now aimed at supporting the hypothesis that molecules that increase the release of norepinephrine and / or serotonin may make subjects less sensitive to life events and reduce the risk of depressive relapse. Lastly, it should also be noted that there are no antidepressants that can improve the anhedonia that is inherent to depressive illness. Moreover, the use of antidepressants now largely exceeds the treatment of depression and this therefore raises the problem of knowing what is actually an antidepressant compared to conventional anxiolytics such as benzodiazepines, or even buspirone. It is possible that we do not yet have at our disposal “real antidepressants” insofar as the derivatives that we currently use are active in the first weeks of treatment in a depressive, on
Are Antidepressants Mood Agents Or Anxiolytic Drugs?

the anxiety disorders and the disorders of sleep associated with depression and that it takes 6 weeks to get a clear improvement in mood. Will the new antidepressants be drugs that can, through an action on transduction signals such as G proteins, modify mood disorders? Are classic antidepressants only anxiolytics? It is possible that in the next decade, a new classification of psychotropic drugs is based on the activity of drugs on mental diseases better identified. This would be a good return since these drugs have been shown to be useful for better understanding the neurobiology of mental disorders.

References


Citation: Bourin M (2018) Are Antidepressants Mood Agents Or Anxiolytic Drugs? SOJ Pharm Pharm Sci, 5(3) 1-6. DOI: 10.15226/2374-6866/5/3/00185

Page 5 of 6


