

The Antidepressants Short Story

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Abstract

Review Article

The number of individuals suffered from depression is constantly increasing worldwide. The antidepressant monoaminergic hypothesis has dominated the pathophysiology of mood disorders and the development of novel treatment strategies for long years, but the discovery of the antidepressant action of ketamine and these metabolites has opened a new way for discovering a fast antidepressant but without reducing side effects. The target of fast and best tolerated antidepressant appears difficult but close.

Keywords: Antidepressants Short Story.

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INTRODUCTION

The number of individuals affected by depression at global level increased by 18.4% between 2005 and 2015. Currently, more than 300 million people are estimated to suffer from depression [1].

After the discovery of antidepressants that were rather accidental, the research has made in meanwhile a tremendous progress and became more targeted. Yet, a long way still to go as researchers still dream of a more effective and a better tolerated antidepressant.

The pharmacological treatment for major depression is based on drugs targeting the monoaminergic system [2, 3]. The most promising solution for this challenge emerged at the beginning of the 21st century, when for the antidepressant effects of the glutamatergic agent, ketamine was decoupled [4].

First antidepressant generation

The first drugs defined and called antidepressants were iproniazid [classified as a monoamine oxidase inhibitor (MAOI)] and imipramine (classified as a tricyclic antidepressant TCA). Their discovery and development were simultaneous.

Imipramine, the first to be clinically in use (TCA), was discovered by Kuhn in 1957, who found out that patients with endogenous depression showed

remarkable improvement after ~ 1 to 6 weeks of daily therapy [5]. By the end of the same year, it was released for clinical use under the brand name Tofranil [5, 6].

In 1957, psychiatrists from Rockland State Hospital presented results showing the effectiveness of iproniazid at non-tuberculosis depressed patients [7]. Just one year later, more than 400 000 patients had been treated at this drug for depression [8].

The first formulation of the biological theories of depressive disorder was possible by the discovery of the action mechanisms of iproniazid and imipramine.

In 1952, the team led by Ernst Albert Zeller observed for the first time that iproniazid was capable of inhibiting MAO [9]. Seven years later, Sigg observed the potentiation of noradrenaline (NA) by Tofranil® (imipramine) [10]. Finally, in 1965, Schildkraut, noticed low levels of epinephrine and norepinephrine in the central nervous system (CNS) of depressed patients and thus suggested the catecholamine hypothesis of depression [11, 12].

Several other MAOIs were introduced on the market after 1957 [13]. Despite being one of the only alternatives for treating depression, the hepatotoxicity and the hypertensive crisis caused by drugs such as iproniazid and pheniprazine made this drug category outdated [9].

In 1961, other tricyclics such as amitriptyline were synthesized by modifying the structure of imipramine [32], desipramine was introduced in 1964 as the active metabolite of imipramine [14]. In 1963, nortriptyline was approved in Great Britain, followed by trimipramine, protriptyline (1966), iprindole (1967), dothiepin and doxepin (1969) [15]. Despite being less tolerated due to its higher adverse effects, TCAs are still among the most frequently prescribed drugs in the world [16,17].

Serotonin reuptake inhibitors

In 1967, Coppen, based on experiments on animals, suggested that 5-HT was a more important neurotransmitter in depression than NA [7, 18, 19].

The monoaminergic theories of depression led to a targeted and planned methodology searching for new antidepressants. The pharmaceutical company Eli Lilly created a 'serotonin-depression study team' [7] who's search for molecules that could selectively inhibit the reuptake of serotonin with better profile tolerance [20].

In 1972, fluoxetine hydrochloride was designated to be the most powerful serotonin selective reuptake inhibitor (SSRI) among all developed compounds [21]. In December 1987, the Food and Drug Administration (FDA) approved the fluoxetine clinical use under the name of Prozac, after a series of clinical studies confirming its equivalent effectiveness to TCAs yet with fewer adverse effects [7, 22].

By 1990, Prozac was the most widely prescribed drug in North America and, in 1994, it was the second biggest selling drug in the world. It was the fastest growth of psychotropic drugs use in the history [7], Called the 'Prozac Boom' [23].

However, four other SSRIs were released in the market; citalopram (Lundbeck, 1989), fluvoxamine (Solvay, 1983), paroxetine (AS Ferrosan, Novo Nordisk, 1991) and sertraline (Pfizer, 1990) [7].

Even though SSRIs dominated the antidepressant market, not all expectations were fulfilled. the SSRIs still had side effects; they interfere with sex and appetite, cause nausea and vomiting, irritability, anxiety, insomnia and headaches [2].

In the hope to reduce the rates of SSRI side effects, other antidepressants emerged during the 1990s, one of the first was venlafaxine (a selective noradrenaline and serotonin reuptake inhibitor), other drugs of the new series included nefazodone (selective serotonin-5HT_{2A} receptor blocker, a weak 5-HT reuptake inhibitor, structurally and pharmacologically related to trazodone) and mirtazapine (α ₂-adrenoreceptor blocker, pharmacologically related to mianserin), and one of the last was reboxetine (a

selective noradrenaline reuptake inhibitor) [2,13]. Although the hopes, these new drugs elicited different rates of side effects but with no improvement in efficacy [2].

The dilemma

The monoaminergic hypothesis of depression still subject of many questions; the delayed clinical onset of antidepressant effect, from 2 to 4 weeks, opposes the data of several studies showing a fastest increase in monoamines in the synaptic cleft right after the treatment start (24). Additionally, acute depletion of tryptophan, serotonin's precursor, decrease the serotonin levels in the brain but does not induce a depressive-like behavior in healthy humans [25-27].

This evidence shows that much more than monoaminergic neurotransmitter levels should be targeted in the brain of depressed individuals [28].

Ketamine and perspectives

In 2000, Berman showed for the first time that it was possible to obtain antidepressant effects in hours and up to 3 days with a reduced dose of ketamine [4]. Since a new treatment of major depression, was found [28].

The mechanism responsible for ketamine's antidepressant effects goes beyond the antagonism of glutamate on the N-methyl-D-aspartate receptor (NMDA receptor). It involves a multistep and complex cascade of events relying on different molecular targets [28]. Ketamine brought new ideas to the research of the neurobiology of depression [29, 30].

The psychotomimetic and dissociative effects of ketamine, and high potential abuse are difficult to overlook, making it not suitable for wide clinical use [28].

Ketamine has an active metabolite, hydroxynorketamine, who can produce a rapid and sustained glutamatergic stimulation [31]. Nevertheless, it could be free of the many safety problems associated with ketamine, and thus, deserve to be studied closely.

Another way is the S-enantiomer of ketamine (S-ketamine or esketamine, especially intranasal), has a 3-4 times greater affinity than ketamine for the NMDA receptor [32]. It was approved by the U.S. Food and Drug Administration (FDA) in March 2019 for treatment-resistant depression. However, the effects of prolonged esketamine therapy still preliminary. when considering its abuse potential, its use should be carefully monitored [33-35].

Identifying the cellular targets of rapid-acting agents, like ketamine, could help develop more interesting antidepressant molecules, by revealing other

receptors implicated in GABA regulation and glutamate transmission [36].

CONCLUSION

A purely neurotransmitter-based explanation for antidepressant drug action still challenged by the significant percentage of patients who's never achieves full remission.

This evidence shows that much more than monoaminergic neurotransmitter levels should be targeted in the brain of depressed individuals. From where the target of research and development of novel antidepressants still neurotransmitters and their receptors.

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