NON-MONOAMINERGIC APPROACHES
IN SEARCH OF NOVEL ANTIDEPRESSANTS

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Depression is a common disabling mental illness which affects millions of people each year and impairs all aspects of everyday life (Murray and Lopez 1996). The burden of the disorder is progressively increasing and the World Health Organization has considered that it will become in the 2020 the second worldwide cause of disability with heavy economic burden for the western societies (Lopez and Murray 1998).

The serendipitous discovery of the first antidepressant dates back to 1950s when two compounds, iproniazide and imipramine, were found to improve the mood of depressed subjects. Then, it was demonstrated that the mechanism of action of iproniazide was the inhibition of the monoamine oxidases, while that of imipramine the inhibition of the reuptake of the monoamines serotonin (5-HT) and norepinephrine (NE). Following this evidence, the enhancement of monoamine neurotransmission was considered the putative mechanism of action of every antidepressant agent, and several monoamine oxidase inhibitors (IMAOs) and trycyclic antidepressants (TCAs) were developed on this basis and successfully used for the treatment of the disorder (Stahl 2008). All this work was based on the monoamine hypothesis of depression which hypothesizes that the disorder results from alterations in the monoamine neurotransmitter systems (monoamine deficiency, alterations of monoamine receptors). However, after decades of research, data supporting the postulated depression-related monoamine alterations are inconclusive and the monoamine hypotheses does not seem sufficient to explain the whole picture of MDD (Marazziti et al. 2009).

More recently, the discovery of the selective serotonin reuptake inhibitors (SSRIs) and the dual-acting serotonin/norepinephrine reuptake inhibitors (SNRIs) allowed to improve treatment and quality of life of depressed patients with relevant advantages on IMAOs and TCAs, especially in terms of side effects. Nevertheless there are still relevant unmet clinical needs: the future generation of antidepressants should lack of the side effects which more commonly lead to discontinuation, in particular sexual dysfunctions and weight gain; the latency of antidepressant effect is another issue that deserve to be addressed and overcome, especially to avoid early discontinuations due to lack of efficacy and to more quickly reduce the risk of suicide; there is a subset of patients who do not respond to the current antidepressants or relapse after an initial improvement or after a sustained period of remission, even if the drug is continued. In fact, although the current antidepressants are effective in about two thirds of patients and they have demonstrated their superiority to placebo (33% of response), the pharmacological treatment of the disorder is far from being satisfactory and remains one of the major cause of morbidity and disability worldwide (WHO 2010). A number of new approaches have been developed in order to optimize the pharmacological treatment of the disorder. One was improving the current pharmacological modulation of the monoamines by the use of triple monoamine reuptake inhibitors or by adding other pharmacological selective action on specific receptor subtypes in order to increase the clinical efficacy and/or decrease the side effects, as in the case of agents combining the serotonin-reuptake inhibition with 5-HT1A or α-2 antagonism which could lead to a faster and stronger clinical efficacy being 5-HT1A and α-2 somatodendritic inhibitory autoreceptors (Kinney et al. 2000).

The focus of research also moved towards non-monoaminergic molecular mechanisms potentially involved in the pathophysiology of depression, including glutamatergic and melatonergic neurotransmission, neuropeptides, glucocorticoids,
opioids, endocannabinoids, inflammatory and neurodegenerative pathways, and intracellular second messengers (Marazziti and Catena-Dell’Osso 2008, Paschos et al. 2009, Zarate et al. 2010, Catena-Dell’Osso et al. 2011). This line of research led to development of several agonist and antagonist agents which have been studied in both animals and humans. Up to now, the only non-monoaminergic drug approved for the treatment of depression is agomelatine, a high affinity agonist of melatonin 1 and 2 receptors, which has shown fast and consistent antidepressant action. Although several other agents, including neurokinin 1 receptor and corticotropin release factor 1 receptor antagonists, entered clinical trials and provided promising results, data are controversial and, so far, no antidepressants have come out from this line of research. There is an urgent need of a more specific psychiatric diagnostic classification system, which identified more phenotypically homogeneous groups of patients. This could enhance the chance to find the pathophysiological mechanisms underlying psychiatric symptoms/disorder and to discover novel therapeutic agents for their treatment.

References
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