Molecular Mediators of Depression Pathophysiology and Treatment: Neuroscience-Based Approaches for Personalized Care

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Depression is a complex multidimensional disorder affecting around 20% of the world population and is now the leading cause of disability worldwide [1]. Although much improvement has been done on the comprehension of depression's pathophysiology, this hasn't been reflected yet in the clinical setting, as depression prevails as one of the world's major public health concerns [2,3]. This is a complex and heterogeneous clinical entity [4] that may overlap with other neuropsychiatric disorders, such as anxiety disorders [5]. Moreover, the diagnosis of depression is based on relatively subjective evaluations of symptoms, relying exclusively on clinical presentation information. Also, the reason why some patients respond well to some of the currently available therapeutic options while others don't, remains pretty much unclear. In this sense, the stratification of patients based on specific pathophysiological characteristics would indubitably have major implications for the diagnosis and treatment of this disorder, towards a more personalized approach. But do we have enough preclinical and clinical data to support the use of pathophysiological biomarkers for the categorization of depressive patients? And if so, can we take advantage of the singularities of each currently available antidepressant therapy? At this point certainly not, but it is reasonable to envision that this is the way the field will evolve. Several studies have supported this view suggesting that, for instance, peripheral markers, such as cortisol levels [6], and inflammatory response molecules levels [7], as well as neural connectivity patterns [8,9] may allow the identification of patients' subgroups and at risk for treatment non-response to first line treatments.

Since the serendipitous discovery of the first antidepressant molecules, in the 1950's, many other drugs with similar antidepressant properties have emerged [10]. Strikingly, the advent of novel antidepressants development has dropped massively in recent years [11], and the field is still lacking effective drugs for a great proportion of patients. This poses a major problem for an ever growing "depressed society". Indeed, not only currently available antidepressant treatments are ineffective in a significant proportion of the depressed patients but also relapse rates are high, emphasizing the need for better therapeutic strategies. Newer antidepressants were developed to be more selective for their neurochemical targets, being thus undeniably safer than those developed back in the 1950's. Nevertheless, there's a lack of mechanistic novelty in the way that, despite a few exceptions, most antidepressants primarily target monoaminergic neurotransmission. Paradoxically, we have been watching the dawn of new hypotheses on the pathophysiology of depression and appreciating that antidepressants mechanisms of action go considerably beyond those initially assumed. In fact, the knowledge on the neurobiological mechanisms underlying depression has progressed substantially in the last years, partly due to animal models of depression. Studies from our group and others have shown that these are useful and robust approaches to understand the mechanisms of action of currently available antidepressants [12-15] but also to explore novel therapeutic opportunities [16-18], when used with an understanding of its limitations.

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Treatment resistance and the delayed onset of action of clinically prescribed antidepressants represent additional major challenges in this field [19]. The oversimplification of depression pathophysiology as solely a neurochemical imbalance disorder has biased the research of new antidepressants for decades. Fortunately, it is now recognized that depression is a systems disorder affecting neural plasticity and brain connectivity [9,12,15,20], and that the currently available pharmacological approaches have a rather limited action. Specifically targeting these networks may foster the development of more effective treatment options for refractory patients. Regarding novel putative targets and therapeutic strategies under investigation, one may highlight the modulation of glutamatergic signalling [21], the resynchronization of circadian rhythms [22,23], and the prominent, previously underestimated, role of the gut microbiome [24,25].

Taking into account the higher prevalence of depression in women compared to men [26], and the evident bias on research towards male preclinical studies, it is urgent to re-orientate the focus in the field and invert this trend. Likewise, emerging data have disclosed sex differences in the response to stress at several levels including, molecular and cellular responses, activation of brain circuits, neural plasticity mechanisms and therefore, behavioral outcomes [27-30].

Recognizing that depression has a biological basis represented a major step for research in this field, as it implied the shift to a neuroscience-based approach of this formerly underestimated medical condition. Hopefully, by integrating preclinical and clinical data, we will reach a stage where we can specifically pinpoint the underlying imbalances and try to develop personalized care to restructure faulty circuits in the depressed brain.

Conflict of Interest

The authors declare no conflict of interest.

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