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Non-Monoaminergic Targets for the Development of Antidepressants: Focus on Neuropeptides

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Abstract: In the last decades, no significant paradigm shifts in the psychopharmacology of major depressive disorder (MDD) have occurred. In fact, after the serendipitous discovery of the first antidepressant, the poor understanding of the pathophysiology of the illness has deeply limited the development of novel antidepressant agents. Although the discovery of the selective serotonin reuptake inhibitors and the dual-acting serotonin/norepinephrine reuptake inhibitors allowed to improve the treatment of MDD, there are still important unmet clinical needs, as the long latency of antidepressant action, the presence of relevant side effects and the lack of efficacy. In fact, even though the available antidepressants have consistently improved the prognosis of the disorder, the pharmacological treatment of MDD is far from being satisfactory and the disorder remains one of the major causes of morbidity and disability worldwide. Recently, besides the classical research involving the monoamines, other non-monoaminergic molecular mechanisms have been explored in search of new antidepressants. Amongst them, the investigation of the central neuropeptides, including substance P, corticotropin-releasing factor, neuropeptide Y, vasopressin and oxytocin, galanin and melanin-concentrating hormone, is increasingly attracting the attention of researchers worldwide. A number of novel compounds acting on neuropeptide receptors have been developed and tested in both animals and humans with different results. In this review, we provided a synthetic overview of the main neuropeptides, going through biochemical and molecular aspects up to preclinical and clinical evidence which link these molecules to the presence of MDD.

Keywords: Antidepressants, corticotropin-releasing factor receptor antagonists, galanin, major depressive disorder, neurokinin receptor antagonists, nemifitide, neuropeptides, vasopressin receptor antagonists.

INTRODUCTION

Major depressive disorder (MDD) is a common disabling mental illness which affects millions of people each year and impairs all aspects of everyday life [1]. In the last years, the burden of the disorder has progressively increased so that it is estimated by the World Health Organization that it will become the second cause of disability worldwide with a heavy economic burden for the western societies [2].

The serendipitous discovery of the first agent with antidepressant action dates back to 1950s when it was demonstrated that two compounds, iproniazide and imipramine, could improve the mood of depressed subjects. Subsequently, iproniazide was found to act through the inhibition of the monoamine oxidases, while imipramine through the inhibition of the reuptake of the monoamines serotonin (5-HT) and norepinephrine (NE). Since then, the enhancement of monoamine neurotransmission has been considered the putative mechanism of action of every antidepressant agent, and a number of monoamine oxidase inhibitors (IMAOs) and triciclic antidepressants (TCAs) have been developed on this basis and successfully used for the treatment of MDD [3].

The monoamine hypothesis of MDD, which postulates that the disorder would result from alterations in the monoamine neurotransmitter systems (monoamine deficiency, alterations of monoamine receptors), has been the object of several investigations [3]. However, data supporting the postulated MDD-related monoamine alterations are inconclusive and the monoamine hypotheses do not seem sufficient to explain the whole picture of MDD [4]. Although the discovery of the selective serotonin reuptake inhibitors (SSRIs) and the dual-acting serotonin/ norepinephrine reuptake inhibitors (SNRIs) allowed to improve the quality of life of MDD patients with relevant advantages on IMAOs and TCAs, especially in terms of side effects, there are still relevant unmet clinical needs. In particular, 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 the antidepressant action is another issue that deserve to be addressed and overcome, especially to avoid early discontinuations due to lack of efficacy and to more quickly

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reduce the risk of suicide. In addition, there is a subset of MDD 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 [3]. In fact, although in controlled clinical trials the available antidepressants, which are effective in about two thirds of patients, have demonstrated their superiority to placebo (33% of response), the pharmacological treatment of MDD is far from being satisfactory and the disorder remains one of the major cause of morbidity and disability worldwide [5].

Several new approaches have been developed in order to optimize the pharmacological treatment of MDD. One consists in improving the current pharmacological modulation of the monoamines by developing 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-$HT1_A$ or α-2 antagonism which could trigger a faster and stronger clinical efficacy being 5-$HT1_A$ and α-2 somatodendritic inhibitory autoreceptors [6, 7].

On the other hand, in parallel to the aforementioned novel monoaminergic pharmacological strategies for antidepressant development, the focus of research moved towards other non-monoaminergic molecular mechanisms potentially involved in the pathophysiology of MDD [8-11]. Amongst them, the investigation on the central neuropeptides is increasingly attracting the attention of researchers worldwide and led to some promising results [10].

Neuropeptides are small protein-like molecules produced by neurons to communicate each other. These peptides, which include substance P (SP), corticotropin-releasing factor (CRF), neuropeptide Y (NPY), vasopressin (VP) and oxytocin (OT), galanin (Gal) and melanin-concentrating hormone (MCH), act as neurotransmitter or co-transmitter through the binding to specific metabotropic or G-protein-coupled receptors. The modulation of monoaminergic neurotransmission is one of the mechanisms by which neuropeptides work in MDD [12]. Moreover, neuropeptides are known to play a pivotal role in the regulation of the response to stressful stimuli. The activation of the stress system is fundamental for survival to internal or external threats to the physiological homeostasis. A rapid counter-regulation of the system is equally important for reestablishing the basic physiology of the organism when the stressful threat ends. It is known that genetic abnormalities, early stressful experiences and exposure to traumatic, unpredictable stress in general might increase the sensitivity to stress and reduce the "resilience" in coping with stressful life events [13]. Neuroendocrinological data demonstrated that the so-called stress-related disorders, which include mood and anxiety disorders, are accompanied by alterations of the stress system [14]. In particular, the hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis with impairment of the physiologic negative feed-back mechanism is one of the most replicated biological correlates of MDD [15]. The brain structures mainly involved in the control of the activity of the HPA axis are the amygdala, the hippocampus and the prefrontal cortex which regulate, in a counter-balancing way, the functioning of the axis just through a number of regulatory central neuropeptides [10]. In addition, some of these neuropeptides seem to be involved in the pathophysiology of MDD independently from the HPA axis. For example, preclinical data indicate that CRF and VP may induce depressive behavior in a way sometimes independent from the hypothalamic function [16-18].

Preclinical studies using animal models of depression reported alterations of the behavioral responses after genetic manipulation of neuropeptides [12, 19]. Further, a number of novel compounds acting on neuropeptides receptors have been developed and tested in both animal models and MDD patients [12] (Table **1-3**). Amongst them, neurokinin (NK) 1 receptor and CRF1 receptor antagonists are those providing the most promising results. In this narrative review, we provided a synthetic overview of the main neuropeptides, going through biochemical and molecular aspects up to preclinical and clinical evidence which links these molecules to the presence of MDD.

SUBSTANCE P

SP is a 11 amino acid peptide belonging to the tachykinin family, which includes several peptides which have been characterized by the presence of the C-terminal pentapeptide Phe5-Xaa4-Gly-Leu-Met-NH_2 [20]. Tachykinins are involved in the central control of several peripheral autonomic functions, such as blood pressure, respiration, micturition and gastrointestinal motility, as well as of other physiological functions as drinking behavior and food intake, mood, anxiety, aggression, pain, learning and memory [20]. They act through the binding to three G-protein coupled receptors, called NK1, 2 and 3. The tachykinin receptor with higher affinity for SP is the NK1 [20]. SP is generally co-synthesized, co-localized, and co-secreted with neurokinin (NK) A but it may also act as co-transmitter with monoamines, such as 5-HT [21]. Monoaminergic neurons receive SP innervation and posses NK1 receptors or they are in close apposition to NK1-containing cells. NK1 receptors are expressed in brain regions involved in the regulation of affective behaviours and the neurochemical response to stress. For these reasons, it has been hypothesized that the antidepressant action of NK1 receptor antagonists may result from the modulation of monoaminergic systems [21].

There is evidence that SP and its receptors may be involved in the pathophysiology of MDD and of anxiety disorders [22-24]. In fact, higher SP cerebrospinal fluid (CSF) levels and lower orbitofrontal cortex NK1 receptor density have been found in MDD patients, as compared to healthy controls [23, 24]. In a 6 weeks trial, carried out in 200 MDD patients, the NK1 receptor antagonist aprepitant (MK-869) was used at a dose of 300mg/day and compared to paroxetine 20 mg/day and placebo (Table **1**). Aprepitant and paroxetine were significantly more effective in the treatment depression and anxiety than placebo, as revealed by the scores of the Hamilton Rating Scale for Depression (HRSD) and Anxiety (HRSA) [22]. In a subsequent study, carried out in about 130 MDD patients, another NK1 receptor antagonist, the L-759274 compound, led to a significantly greater improvement of HRSD scores than placebo [25]. Unfortunately, in other randomized, double-blind, controlled studies

Table 1. Clinical Trials with NK1 Antagonists in Depressed Patients

Author	Drug	Design of the Study	Subjects N	Doses mg/day	Main Findings
Kramer 1998 [21]	MK-869 o aprepitant	6-week, double-blind, randomized, comparison with placebo and paroxetine 20 mg/day	200	Fixed dose 300	Aprepitant and paroxetine were significantly superior to placebo; both active treatments were of equal efficacy.
Kramer 2004 [25]	L-759274	6-week, double-blind, randomized, placebo-controlled	130	Fixed dose 40	Significantly greater improvement in HRSD scores than placebo.
Keller 2006 [26]	MK-869 o aprepitant	8-week, randomized, double-blind, multicenter trial, comparison with placebo and paroxetine 20 mg/day	2500	Fixed doses 80 and 160	No statistically significant differences from placebo were observed at week 8 for either dose of aprepitant; conversely, paroxetine 20 mg was significantly more effective than placebo.
Ratti 2011/a [27]	Casopitant	8-week, double-blind, randomized, placebo-controlled	356	Fixed doses 30 and 80	Casopitant 80 mg but not 30 mg achieved statistically significant improvement versus placebo.
Ratti 2011/b [27]	Casopitant	8-week, double-blind, randomized, comparison with placebo and paroxetine 30 mg/day	362	Fixed dose 120	Neither casopitant nor paroxetine achieved statistical separation from placebo at end point.

involving about 2500 MDD patients, aprepitant at doses of 80 mg/day and 160mg/day showed a lower efficacy than paroxetine and it did not show any benefit over placebo [26]. The possible role of NK1 receptor antagonists in the treatment of MDD is still an area of active debate. Recently, another NK1 receptor antagonist, casopitant, at a dose of 80 mg was found to be significantly superior to placebo, as revealed by the scores of the HAMD17, while supporting the hypothesis that some MDD patients may benefit of the use of NK1 receptor antagonists [27] (Table **1**).

CORTICOTROPIN-RELEASING FACTOR

CRF, a 41 amino acid peptide isolated by Vale *et al*. in the 1981, is involved in the regulation of neuroendocrine, autonomic and behavioral responses to environment being fundamental for the modulation of the stress response and for the maintenance of the physiological homeostasis [28, 29]. In fact, CRF is the main regulator of both, basal and stress-induced HPA activity trough the binding to two specific high-affinity G protein-coupled receptors, the CRFR1 and CRFR2 [30]. Of note, there are several other CRF-related peptides, called urocortins (UCNs) that exert complementary or sometimes contrasting actions in the complex process of stress adaptation [31]. UCNs influence several physiological functions via paracrine or autocrine activation of the CRFR1 and CRFR2 [30]. The highest concentrations of these receptors were found in the brain stem, limbic system, and cortical regions, all areas involved in the regulation of mood and anxiety, with CRFR1 being the most abundant subtype in the limbic regions and the pituitary [32]. In the central nervous system (CNS), CRF is involved in the regulation of the adaptive behavioral, cognitive, neuroendocrine, autonomic, and immunologic responses to aversive stimuli.

In the last decade, a number of CRFR1 antagonists have been developed, including DMP696, R121919, CP-154526 GSK561679, GW876008, GSK586529, TAI-041/JNJ19567470, SSR125543, NBI-34101, ONO2333Ms, CP-316311, antalarmin and pexacerfont [29]. Overall, they showed consistent anxiolytic-like effects in animal models of anxiety, as conditioned fear, shock-induced freezing and neonatal isolation in rodents [17]. Encouraging results also came from studies using animal models of depression: in particular, DMP696, R121919 and antalarmin were found to reduce the forced swim immobility in mice [33, 34], and to reverse the impairment of hippocampal neurogenesis in a chronic mild stress model [17, 18, 35]. However, data are not univocal and, in other studies, the same compounds did not show any antidepressive-like action [36-37]. The same is true for the CP-154526 compound firstly reported to have antidepressant-like effects in the learned helplessness paradigm, but subsequently failing to replicate this result [38, 39].

Since 2000, CRFR1 antagonists entered clinical trials (Table **2**). In the first, open-label, trials, R121919 showed a good overall safety profile and a good efficacy in reducing depressive and anxiety symptoms of MDD patients [40, 41]. On the contrary, the compounds ONO2333Ms and CP-316311 did not show any antidepressive action in a double-blind, placebo-controlled trial [42]. Currently, other CRFR1 antagonists, including GSK561679, GW876008, GSK586529, TAI-041/JNJ19567470, SSR125543, NBI-34101, antalarmin and pexacerfont, are under investigation or have completed efficacy trials for MDD. Data from these undergoing trials will allow to achieve relevant conclusions regarding the potential of CRFR1antagonists for the treatment of MDD.

NEUROPEPTIDE Y

NPY is a 36 amino acid, amidated peptide, which is present in the central and peripheral nervous system and can act as co-transmitter, neuromodulator and neurohormone [43]. Central NPY has several physiological functions, including the modulation of the stress response, circadian rhythms, feeding and reproductive behaviors [43]. NPY has been

Table 2. Clinical Trials with CRF1 Antagonists in Depressed Patients

Author	Drug	Design of the Study	Subjects N	Doses mg/day	Main Findings
Zobel 2000 [40]	R121919	Observational	24	Flexible doses 5-40 and 40-80	R121919 was safe and well tolerated; significant reductions of depression and anxiety scores; clinical profile comparable to that of paroxetine.
Kunzel 2003 [41]	R121919	Observational	24	Flexible doses 5-40 and 40-80	No serious side effects or impairment of the hypothalamic-pituitary-gonadal system, the hypothalamic-pituitary-thyroid axis, the renin-angiotensin system, prolactin or vasopressin secretion, no changes in the serum corticotropin and cortisol concentrations.
Binneman 2008 [42]	CP-316,311	6-week, double-blind, randomized, comparison with placebo and sertraline 100 mg/day	123	Fixed dose 400 twice daily	No significant differences between the CP-316,311 and placebo groups, while sertraline showed higher efficacy.

found to exert anxiolytic effect through the postsynaptic Y1 receptors and anxiogenic effect through the presynaptic Y2 receptors. In mice, when injected into the amygdala, it has shown relevant anxiolytic effect [44], while NPY knock-out genotypes exhibit more anxious phenotypes [45]. Partial deletion of Y1 receptors has been found to increase anxiety [46], while suggesting that the anxiolytic properties of NPY was mediated by these receptors subtype. On the contrary, the stimulation of Y2 receptors seems to have anxiogenic effect [47]. In fact, intracerebroventricular injection of the Y2-selective antagonist BIIE0246, or deletion of Y2 receptors, resulted in anxiolytic and antidepressant-like effects [48, 49]. In addition, region-specific alterations in central NPY levels have been detected in animal models of depression and after antidepressant administration [44].

In humans, plasma NPY levels seem to rise after stress exposure [42, 43] and their increase was found to be negatively related with the experienced psychological distress [50]. Decreased CSF and plasma NPY levels were reported during acute MD episode [44, 51]. However, a subsequent study, involving 28 medication-free patients with remitted MDD and 26 healthy control subjects undergoing tryptophan depletion and sham depletion, did not find abnormalities in plasma NPY levels [52].

Taking into account the role of NPY in stress and stress-related disorders, the searching for agonists and antagonists of its receptors could represent an interesting novel avenue for discovering compounds with anxiolytic and/or antidepressant actions.

VASOPRESSIN AND OXYTOCIN

VP and OT are nonapeptides constituted by a cyclic part of six amino acid and a three-residue tail alpha-amidated at the COOH-terminal. VP differs from OT in terms of two amino acids (Phe vs Ile at position 3 and Arg vs Leu at position 8, respectively). They are mainly synthesized in the magnocellular neurons of the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus, and they are targeted along the axons to the posterior pituitary [8]. Besides a number of physiological functions, VP and OT play a role on the modulation of the endocrine stress response [53, 54].

VP acts as regulator of ACTH responses by potentiating the stimulatory effect of CRF trough the binding to specific G protein-coupled receptors, the V1b receptor subtype [55]. The first specific non-peptide V1b receptor antagonist, the SSR149415 compound, opened new avenues for exploring and, possibly, treating stress-related disorders [56, 57]. This compound was found to inhibit VP-induced $Ca2^{++}$ increase in Chinese hamster ovary cells expressing V1b receptor and to decrease VP- and restraint-stress-induced ACTH secretion in corticotroph cells in rats [56]. Further, SSR149415 showed antidepressant-like effect in the forced swimming test in both normal and hypophysectomized rats, while in the chronic mild stress, its repeated administration reduced anxiety, despair and the loss of coping behavior produced by stress in mice [16]. In a more recent study, chronic but not acute administration of SSR149415 was shown to normalize olfactory-bulbectomy-induced hyperactivity up to 1 week after cessation of administration, supporting the hypothesis that V1b receptor antagonists could have long-lasting antidepressant activity [58]. Unfortunately, other studies did not confirm these promising results [59, 60] and, at present, no clinical trials using V1b antagonists in MDD patients have been published.

As far as OT is considered, hypothalamic OT reaches the anterior pituitary through the hypothalamic-pituitary portal vascular system where it acts as regulating factor of prolactin, ACTH and gonadotropins trough the binding to a specific class I G protein-coupled receptor [61]. Since OT can decrease anxiety levels and, more in general, the endocrine response to environmental stressors, as well as modulate cognitive functions and promote positive social relationships, some symptoms of depression, including social withdrawal, cognitive impairment, appetite modifications and stress

reactivity may be influenced by dysfunction of the OT system [62, 63].

Promising results have been obtained in preclinical studies using the OT agonist carbetocin [64]. This compound was reported to significantly reduce immobility and increase swimming behavior in the forced swim test, and the effect was blocked by the co-administration of an OT antagonist, while demonstrating that the antidepressant-like effect was mediated by the activation of OT receptors [65]. However, these promising results need to be replicated in order to better understand the real potential of OT agonists for the treatment of MDD.

Another line of research involves Mif-1, also known as L-prolyl-L-leucyl-glycinamide (PLG), which is the tripeptide tail of OT. Although, the available data are too scant to make definitive inference, Mif-1 gave very promising results in terms of efficacy and short latency of antidepressive effect [66-68] (Table **3**). Nemifitide, a pentapeptide analog of endogenous Mif-1, is currently under investigation for the treatment of MDD patients [69-72] (Table **3**). In particular, in a 6-week, double-blind, multicenter, outpatient efficacy study, 81 MDD patients were randomized to receive 30 mg/day, 45 mg/day or placebo. Both nemifitide and placebo were delivered by daily subcutaneous injection for 2 weeks, 5 days per week. Statistically significant higher efficacy, as revealed by the HAMD rating scores, was found for nemifitide 45 mg/day, as compared to placebo, and both doses of nemifitide showed a greater efficacy than placebo in patients with baseline HAMD score >22, with a good tolerability and safety profile [72]. In addition, a recent open-label pilot study, carried out in 25 patients with chronic refractory MDD, reported a high rate (about 50%) of responders as revealed by the scores of the Montgomery-Asberg Depression Rating Scale [70]. Other studies are, however, needed to confirm this preliminary evidence.

GALANIN

GAL is a 30 amino acid peptide which is proteolytically processed from the precursor preprogalanin [73, 74]. It acts by binding three G-protein-coupled receptors, called GALR1, GALR2 and GALR3, and has several physiological functions, including the modulation of pain perception, sleep pattern, food intake, sexual activity, learning and memory [75]. In addition, this neuropeptide, highly expressed in anxiety and depression relevant brain regions, such as the locus coeruleus, amygdala, hypothalamus and pituitary, has been shown to be involved in the modulation of anxious and depressive behaviors [76, 77]. GAL may influence stress-related behaviors by interacting with monoaminergic neurotransmitters (5-HT and NE) and with g-aminobutyric acid [78-82]. Further, GAL seems to have a significant impact on HPA axis functioning, while inhibiting stress-induced ACTH secretion, presumably by altering CRF and/or VP release from the axons in the median eminence [83-86]. In fact, an anatomical and functional connection between GAL, CRF and VP has been observed, as part of the hypothalamic neurons in the paraventricular nucleus co-express these neuropeptides [87-89]. In rats, the intraperitoneal infusion of a non-peptide GAL receptor agonist showed antidepressant-like effects [90]. Recent preclinical data suggest that GALR2 activation has antidepressant-like, anticonvulsant and pro-neurogenetic effects and that stimulation of GALR1 and GALR3 induces depressive behaviors [91-93]. In humans, the intravenous administration of GAL was found to have antidepressant effect in MDD patients under standard antidepressant treatment [94]. At present, it is difficult to say the extent to which GALRs may represent valuable targets for the discovery of new antidepressant agents.

Table 3. Most Relevant Clinical Trials with Mif-1 and/or Nemifitide in Depressed Patients

Author	Drug	Design of the Study	Subjects N	Doses mg/day	Main Findings
Van der Velde 1983 [67]	Mif-1	28-day, double-blind, randomized, comparison with imipramine	20	Fixed dose	Mif-1 as effective as imipramine; antidepressive effect rapid and often dramatic.
Ehrensing 1994 [68]	Mif-1	2-week, double-blind, randomized, placebo-controlled	20	Fixed dose 10	At the end of the first week, patients receiving MIF-1 significantly improved; administration of MIF-1 during the second week to patients who had received placebo during the first week resulted in substantial improvement.
Feighner 2003 [69]	Nemifitide	Open-label study	27	Flexible doses 18 to 72	No clinically significant side-effects were observed; 66.7% responded to treatment.
Montgomery 2006 [72]	Nemifitide	6-week, double-blind, randomized, placebo-controlled, multicenter	81	Fixed doses 30 and 45	Significant higher efficacy of both doses of nemifitide; good tolerability and safety profile.
Feghner 2008 [70]	Nemifitide	Open label	25	Flexible doses 40 to 240	High response rate of more than 50%.

MELANIN-CONCENTRATING HORMONE (MCH)

MCH is a 17 amino acid cyclic peptide discovered in 1983 which acts through the binding to two G protein-coupled receptors, the MCH receptors (MCHR) 1 and 2 [95-97]. While MCH is exclusively expressed in the hypothalamus and zona incerta, MCHR are widely expressed in peripheral tissues and throughout the brain, suggesting the involvement of MCH in a wide range of physiological functions, including the regulation of energy homeostasis and food intake, sleep, reward, mood and anxiety levels [98, 99]. The hypothesis of an involvement of the MCH system in the pathophysiology of MDD came from animal models of depression showing that the MCHR1 antagonist SNAP-7941 could reduce immobility time in the rat forced-swim test with same efficacy of fluoxetine [100]. Subsequently, other MCHR1 antagonists, such as ATC0065, ATC0175, GW803430, and SNAP-94847, were discovered and resulted effective in acute and chronic animal models of depression [101-105]. However, as these compounds also showed various degrees of affinity for both 5-HT2B and 5-HT1A receptors [101], it is difficult to establish the relevance of the binding to MCHR for the antidepressant effect. Further, MCHR1 antagonists have been found to induce hippocampal neurogenesis, which is considered a crucial step for the onset of antidepressant activity [103]. Although, very little is known on the role of endogenous MCH in the regulation of mood, cognition and emotion, the MCHR1 could represent valuable new target for antidepressant development.

CONCLUSION

In the last decades, no significant paradigm shifts in the psychopharmacology of MDD have been occurred. In particular, the development of novel antidepressant agents has been limited by the poor understanding of the pathophysiology of the illness, and serendipity has continued to play a key role in drug discovery. In fact, the limits of the animal models of depression and the inadequacy of the current psychiatric diagnostic classification systems, which do not give precise phenotypic delineations, have dramatically slowed our understanding on the mechanisms leading to MDD.

Beside the classical research on monoamines, neuropeptides, which are involved in the modulation of monoamine neurotransmission and of the stress response, seem to represent an important source of molecular targets for the search of novel antidepressants. At present, this line of research led to development of several agonist and antagonist agents which have been studied in both animals and humans. Although several of these agents have 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 identify the pathophysiological mechanisms underlying psychiatric symptoms and to discover novel therapeutic agents for their treatment.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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