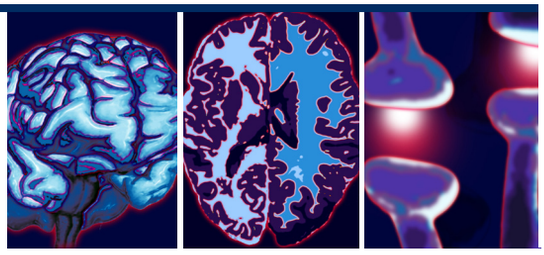
REVIEW



Connection re-established: neurotransmission between the medial prefrontal cortex and serotonergic neurons offers perspectives for fast antidepressant action

Adeline Etiévant[1]*, Laura Lambás-Señas[1]*, Erika Abrial[1], Cécile Bétry[1], Nasser Haddjeri[1] & Guillaume Lucas[†1]

Summary points

- Background
  - Only a third of depressed patients experience a complete therapeutic improvement with the use of current antidepressant treatments.
  - Even when effective, these molecules display a delayed onset of action. This can be a critical point when considering that a significant proportion of patients are at risk for suicide.
  - The development of new, more effective and more rapid antidepressant treatments constitutes a major issue for current neuropsychopharmacological research.
- New perspectives of research
  - Several authors have pointed out a potential role for the molecular factors and/or processes that favor tissular growth and plasticity within the brain, proposing that monoaminergic-based pharmacological approaches might be somewhat outdated.
  - There are, however, a number of recent reports suggesting that the anatomical connections existing between the medial prefrontal cortex (mPFC) and serotonergic (5-HT) neurons located within the dorsal raphé may constitute a promising vector to achieve more rapid and/or more effective antidepressant efficacy. This vector being mobilized by using either pharmacological or surgical tools.
- Importance of the mPFC/5-HT connection
  - Deep-brain stimulation of the human Cg25 area produced strong and rapid antidepressant effects in treatment-resistant depressed patients. Animal experiments indicate that the glutamatergic projections connecting the mPFC and 5-HT neurons appear to be crucial for the expression of such effects.
  - Several animal studies also indicate that the stimulation of 5-HT_4 receptors may result in antidepressant-like effects within a four- to seven-fold more rapid timeframe than what is observed with standard molecules. This effect appears to involve the mobilization of mPFC/5-HT connections.
  - Similarly, the use of 5-HT_7 receptor antagonists led to promising results to achieve a more rapid and/or more effective antidepressant action. Once again, the effect seems to originate from the mPFC, with a possible involvement of the glial system.
- Conclusion
  - A more complete characterization of the mPFC/5-HT relationship should open up new perspectives for the treatment of depression, with the possibility to address multiple targets and therefore increase the diversity of approaches.

[1]EAC-CNRS 5006, Université Claude-Bernard Lyon 1, 8 Avenue Rockefeller, 69373 Lyon Cedex 08, France
[†]Author for correspondence: Tel.: +33 478 777 560; Fax: +33 478 777 209; guillaume.lucas@gmail.com
*Authors contributed equally

part of future medicine fsg

SUMMARY The search for fast-acting antidepressants has been a major challenge in neuropsychopharmacology for many years. Although the involvement of serotonin (5-HT) in the mechanisms of action of classical antidepressants has been clearly established, the delayed onset of action of these drugs prompted several authors to propose alternative targets in order to achieve a more rapid relief of symptoms in depressed patients. However, recent studies indicate that it may be possible to elaborate fast-acting antidepressant strategies based on 5-HT, provided that such strategies would directly target 5-HT neuron electrical activity. Furthermore, glutamatergic pyramidal neurons projecting from the medial prefrontal cortex to the dorsal raphé appear to play a critical role. This article presents some of the data that support this hypothesis, including results from medial prefrontal cortex deep-brain stimulation studies, as well as those related to treatments with 5-HT_4 agonists and 5-HT_7 antagonists.

The search for a rapid-acting antidepressant (AD) strategy is still considered as a "quest for the holy grail" in the field of neuropsychopharmacology [1]. Typical ADs, among which selective serotonin reuptake inhibitors (SSRIs) are the most frequently used, display a delayed onset of action, sometimes requiring administration for several weeks before a clinical improvement can be seen. In addition, their therapeutic efficacy is not entirely guaranteed, as up to two-thirds of patients may be partially or fully resilient to such treatments [2]. The delayed action of ADs becomes a critical factor in particular cases of major/severe depression, where the risks of suicide are strongly increased. Several clinical reports indicate that suicide attempts are maximal during the first weeks of treatment, and that this risk is decreased in patients who experience an earlier AD response [3]. Furthermore, the adherence of patients to their medication appears to be more stable if therapeutic efficacy is perceived to occur rapidly [3]. It is now accepted that, despite the variety of their pharmacological profiles and primary targets, a common trait of all the currently used AD molecules resides in their ability to increase central serotonergic (5-HT) transmission [4–6]. In addition, most studies have focused on the dorsal raphé (DR) nucleus, from which the vast majority of brain 5-HT innervation originates [4]. However, SSRIs (e.g., tricyclics, MAO inhibitors or mixed reuptake inhibitors) do not act directly on 5-HT impulse flow, but induce an indirect augmentation of 5-HT extracellular levels via inhibition of inactivation mechanisms (e.g., reuptake or catabolism). Consequently, their facilitatory effect on 5-HT transmission is fully dependent on the actual level of DR 5-HT neuron electrical activity. Numerous animal studies have shown that, during the early stage (a few days) of a SSRI treatment, the 5-HT neuron impulse flow is quasi-suppressed, owing to the existence of inhibitory somatodendritic 5-HT_{1A} autoreceptors [5,7]. It is only after a long-term (>2–3 weeks) period of treatment that these autoreceptors become desensitized, thus allowing the 5-HT neuronal firing rate to recover; it is thought that the delay of action of ADs is precisely related to the period required for this desensitization to occur [5,7].

More recently, new strategies of research have emerged, with the purpose of 'bypassing' this 5-HT-related inertia. They were oriented toward assessing the effects of AD beyond the postsynaptic 5-HT receptor level, searching for the cellular/molecular mechanisms that were affected by the treatment. An extensive and seminal work has been conducted in this field for more than a decade, in particular by the groups of Duman and Nestler [8,9]. These studies enabled the isolatation of a number of biological parameters that are deeply modified after a sustained AD treatment. Initially, the first changes identified were an activation (phosphorylation) of the transcription factor CREB [10] and enhanced adult neurogenesis [11], both of which are selectively expressed within the hippocampus. More recently, the BDNF (for review see [12]) and VGF [13,14] growth factors were found to play a significant role in the effect of ADs, as well as the MAPK cascade [15] and p11, a Ca^{2+}-binding protein of the EF-hand (helix–loop–helix) type [16,17]. These observations led to the general idea that ADs share the common ability to positively modulate cellular growth and plasticity in mood-related brain areas. As such, they would act in an opposite manner to stressful experiences, which are also known as risk factors for the emergence of depression in humans [18].

Should the emergence of these hypotheses mean that 'old' approaches based on the modulation of neurotransmission, such as

neuropharmacological ones, have to be considered outdated? It has, for instance, been recently proposed that a viral-mediated gene therapy, aimed at increasing brain levels of p11, could constitute a promising new way to achieve AD efficacy [16,19]. Similarly, it is suggested that the development of therapeutic strategies able to directly target the molecular factors mentioned earlier would allow a more rapid onset of action than the currently used ADs [12,20]. Some recent clinical trials have been successful in this context. These studies were notably based on the use of the NMDA antagonist ketamine or consisted of sleep deprivation, both strategies being effective within hours [3]. The idea was to favor a rapid increase of synaptic/brain plasticity, involving, at least partially, an imbalance of the AMPA to NMDA throughput [3]. There is, however, a growing body of evidence that indicates that acting upon the connections existing between different neuronal networks, which includes pharmacological approaches, may also allow fast AD effects. In the present work, we will review the importance of the relationship existing between the medial prefrontal cortex (mPFC) and 5-HT neurons, with a particular focus on the role of 5-HT_4 and 5-HT_7 receptors (some excellent reviews and articles have already highlighted a role for cortical 5-HT_{1A} and 5-HT_{2A} receptors in this context [21–23]). We will first discuss a series of data showing that a direct, intracerebral electrical stimulation of the mPFC itself may result in spectacular AD efficacy in patients, and displays strong AD-like properties in rodents. The importance of central 5-HT transmission in the underlying mechanisms will also be discussed. We will thereafter address the relevance of studying 5-HT_4 receptors, their agonists potentially constituting a new (and yet 'monoaminergic') class of fast-acting ADs. In a similar manner, we will present a body of evidence suggesting that 5-HT_7 receptor antagonists may also be of importance for the purpose of accelerating AD efficacy. For both 5-HT receptor types, as already mentioned, the connection between the mPFC and 5-HT neurons appears to play a pivotal role in the expression of the reported features.

Deep-brain stimulation of the mPFC

Within the human brain, several limbic structures have been associated with affective and anxiety disorders. Historically, ablative stereotactic procedures of the anterior cingulate cortex (anterior cingulotomy), of projections from the orbitofrontal (subcaudate tractotomy) [24,25] and/or cingulate cortex to the basal ganglia and medial thalamus (limbic leucotomy) constituted surgical options for treatment-refractory depression (for review see [26–28]). However, these procedures, although partially effective in alleviating symptoms in patients with affective and obsessive–compulsive disorders, have significant and irreversible side effects [27,29]. More recently, functional imaging studies emphasized the involvement of limbic dysfunction in depression, and revealed decreases in metabolism of dorsal limbic and neocortical regions (prefrontal, premotor and parietal cortex) and relative increases in ventral paralimbic areas (subgenual cingulate, anterior insula, hypothalamus and caudate) in depressed patients [30,31]. Interestingly, the subgenual cingulate gyrus (SCG), adjacent to the Brodmann area 25, is able to modulate the activity of both the frontal cortex and the limbic system, which are respectively underactive and overactive in depressed patients [32–34]. Moreover, it has been reported that this region, involved in the mediation of depressive symptoms [35,36] or acute sadness [37,38], is also metabolically overactive in treatment-resistant depression [39,40] and is normalized after successful treatments including pharmacological treatment [30,32,41], electroconvulsive therapy [42] and transcranial magnetic stimulation [43]. Mayberg *et al.* conducted a pilot study to examine the efficacy of SCG area deep-brain stimulation (DBS) in treatment-resistant patients [44]. In the initial report, four of six patients demonstrated a significant reduction of depressive symptoms after only 1 week of high-frequency DBS. In addition, the authors observed acute, quasi-instantaneous behavioral changes during the daily short sessions of DBS that occurred within the first postoperative week, before the protocol was established in a continuous mode [44]. Therefore, it may be hypothesized that the efficacy of DBS actually occurs within a very rapid time-frame, similar, or even inferior, to the one observed with ketamine or sleep deprivation (see earlier). The recruitment of 14 more refractory patients confirmed these preliminary results: the benefits observed after 1 week on the Hamilton Depression Rating Scale were still maintained after 6 or 12 months of stimulation, with 35% of patients (seven out of 20) in total remission, and 25% (five out of 20) displaying a partial response [45,46]. Additional trials now

need to be conducted in a larger group of patients with the addition of 'true' double-blinded methods of evaluation to fully validate the method. However, it should be mentioned that, although the studies were not blinded as such, they were subject to strict control conditions: during the first postoperative week, patients were stimulated using either a 0.0 V, a subthreshold or the best-set condition of stimulation, being unaware of the setting chosen. In the first two cases, stimulation failed to elicit any behavioral changes. Also, in order to assess whether the long-term benefit in responders could be related to placebo or nonspecific factors, the continuous stimulation of patient one was stopped after 6 months. Following blinded discontinuation of bilateral stimulation (stimulators set at 0.0 V), AD effects were maintained for 2 weeks but a progressive change in behavior, characterized by loss of energy and initiative, impaired concentration and reduced activities were observed during weeks 3 and 4. These symptoms were normalized 48 h after the stimulator was turned back to the previous optimal settings.

Although the neurobiological bases of DBS as a therapeutic AD strategy are not currently determined, several lines of evidence suggest that there are specific neural circuits within the cortico-limbic system that mediate stress responsiveness, mood and emotional regulation. Regarding its mode of action, one of the commonly proposed hypotheses is that high-frequency stimulation reduces neural transmission through inactivation of voltage-dependent ion channels [47–49]. However, currently available animal studies do not support this possibility. Thus, Hamani *et al.* have modeled the antidepressant effect of SCG DBS by stimulating the rat mPFC [50], a brain area that is likely to be homologous to the human SCG in rodents [51]. They clearly demonstrated that high-frequency stimulation of mPFC (130 Hz) produced an AD-like response in the forced swim test, and improved anxiety and hedonic states in both the novelty suppressed feeding test and sucrose consumption test. Importantly, they also showed the involvement of central 5-HT in DBS. First, using microdialysis, they showed that high-frequency stimulation of the mPFC correlated with a sustained increase of hippocampal 5-HT release. Second, AD-like behaviors induced by mPFC DBS are suppressed by a lesion of the 5-HT system. In agreement with these results, it has also been reported in rodents that a moderate to high (20–60 Hz) frequency stimulation of mPFC glutamatergic neurons increases 5-HT release in the DR, as well as dopamine output in both the ventral tegmental area and the nucleus accumbens [21,52–55]. More recently, we have studied the effects of mPFC DBS (130 Hz) on the firing activity of DR 5-HT neurons by using electrophysiological paradigms. We found that after only 1 h of DBS, the mean firing activity of 5-HT neurons increased by 30% [56].

Surprisingly, Hamani *et al.* also observed that a neuronal lesion in the mPFC, induced by using ibotenic acid, failed to affect the AD-like effects of DBS [50], which caused the authors to propose a possible involvement of 'en passage' fibers rather than local cell bodies [50]. Although it can not be excluded that other cortical areas may exert an influence on DR 5-HT activity, it remains that anatomical studies report a dense innervation of the DR coming from the mPFC [57,58]. Accordingly, *in vivo* 'collision' electrophysiological experiments, using orthodromic and antidromic stimulations, have shown that a significant proportion of mPFC cell bodies project directly into the DR [21]. It is therefore possible that the persistence of DBS effects after ibotenic lesion could be caused by the recruitment of the few surviving pyramidal neurons. If so, the activity of these survivors would necessitate a strong metabolic supply, and the role of glial cells becomes more important than in normal conditions. Interestingly, Banasr and Duman have characterized the effects of a pharmacological glial reduction in the mPFC of adult rats in behavioral tests known to be affected by stress or AD treatments [59]. Remarkably, they demonstrated that mPFC infusions of an astrocyte-specific toxin, L-α-aminoadipic acid, induced anhedonia, anxiety and helplessness while a ibotenic acid neurotoxic lesion failed to induce any behavioral impairment [59]. These effects of L-α-aminoadipic acid, similar to chronic unpredictable stress-induced depressive-like behaviors, support the hypothesis that loss of glia contributes to the core symptoms of depression. Based on these observations, we conducted experiments in order to assess the implication of glia in the AD response to DBS. Our preliminary results showed that L-α-aminoadipic acid infusion in the mPFC attenuated the facilitating effect of DBS on 5-HT firing activity [56]. We concluded that the glial system plays an important role in the AD effect of DBS, likely by enhancing

gliotransmitters and glutamate uptake in the mPFC. Indeed, Banasr *et al.* have recently shown that glia-mediated glutamate uptake in the mPFC plays a key role in the behavioral and physiological response to stress and, therefore, in the pathophysiology of depression [60].

While DBS of the mPFC is at the early stage of testing, it seems to be a very promising procedure, owing both to its ability to improve depressive symptoms in refractory patients, and the amazing speed (see earlier) with which it might operate. The characterization of mechanisms mediating these AD effects may provide new perspectives for less invasive and/or pharmacological treatments. Some of these hypotheses are summarized in **Figure 1**.

5-HT$_4$ agonists as a putative new class of fast-acting antidepressants

Since 5-HT$_4$ receptors were first identified in 1988 [61,62], a growing number of studies have been conducted to assess both their

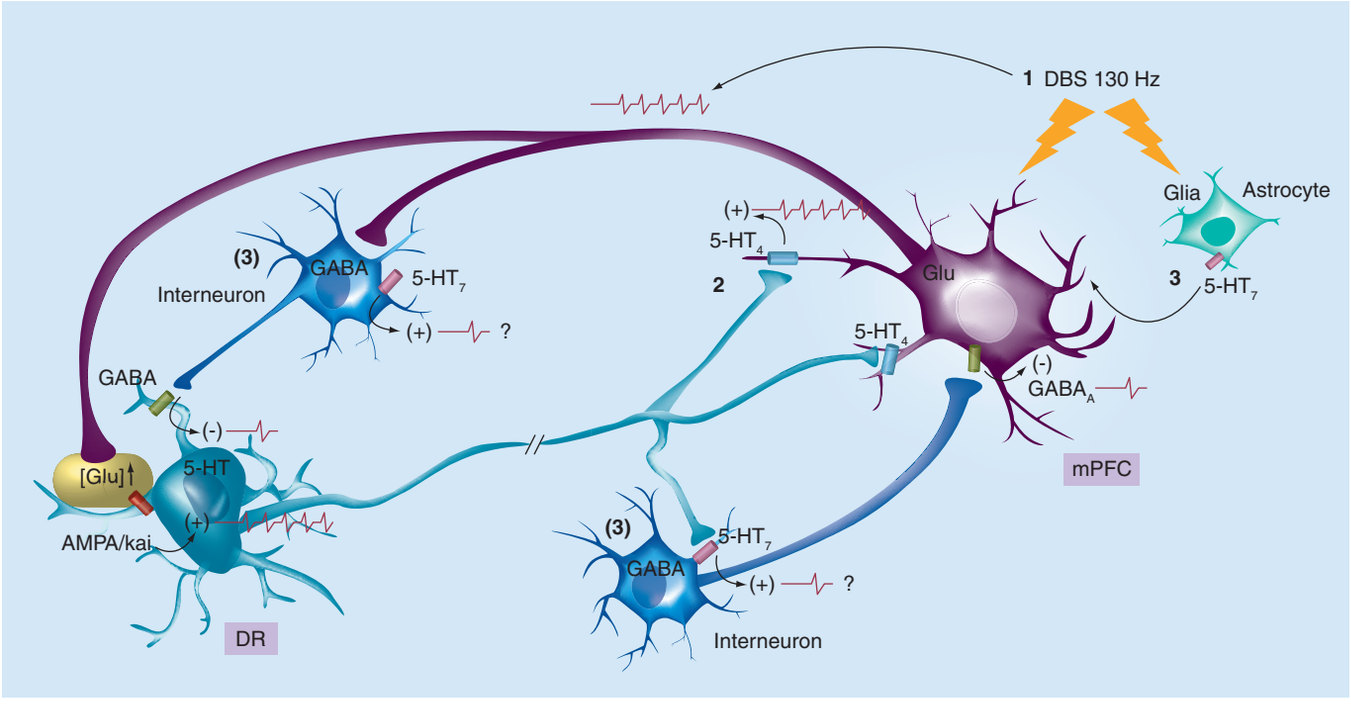


Figure 1. Some hypotheses regarding the mechanisms underlying fast antidepressant responses related to the cortico-raphé neurotransmission. The key factor appears to be the enhanced release of glutamate in the synaptic cleft between pyramidal neuron terminals and DR 5-HT cell bodies. **(1)** High-frequency stimulation (DBS, 130 Hz) of the mPFC leads to an increased firing rate of glutamatergic pyramidal neurons. Consequently, extracellular levels of glutamate augment in the vicinity of 5-HT neurons within the DR, which receive an important innervation from the mPFC. This, in turn, results in an enhanced stimulation of glutamatergic receptors located on 5-HT cell bodies, particularly those of the ionotropic AMPA/kai type, increasing the electrical activity of DR 5-HT neurons. It seems that glial cells (represented here by the astrocyte) contribute to the effect of DBS by allowing the challenged metabolism of the pyramidal neuron to be sustained. **(2)** The stimulation of mPFC 5-HT$_4$ receptors by an agonist also increases the firing rate of pyramidal neurons, in a similar manner to that described for **(1)**. Ultimately, this leads to an enhanced activity of DR 5-HT neurons. **(3)** The blockade of 5-HT$_7$ receptors by an antagonist may also contribute to the excitatory control exerted by mPFC pyramidal cells on DR 5-HT function. Although the precise mechanisms involved remain to be determined, 5-HT$_7$ receptors might play a role in the modulation of the glia–neuron interaction within the mPFC, thus exerting an influence on the ability of pyramidal cells to maintain an increased activity. Alternatively, it is also possible that inhibitory GABA interneurons within the mPFC (and/or the DR) express a certain level of 5-HT$_7$ receptors. As these receptors are usually excitatory, their blockade should induce a disinhibition of pyramidal neurons (and/or 5-HT ones). Whatever the different mechanisms responsible for the antidepressant-like properties of 5-HT$_7$ antagonists, we hypothesize, as in the case of **(1 & 2)**, that they are mediated, at least in part, by an increase of the extracellular levels of glutamate within the DR. (In this model, the role of DR GABA interneurons, which also receive glutamatergic projections from the mPFC is unclear. However, their influence seems to be mostly secondary in the context of a stimulated cortex [21].)
5-HT: Serotonin; DBS: Deep-brain stimulation; DR: Dorsal raphé; Glu: Glutamate; kai: Kainate; mPFC: Medial prefrontal cortex.

physiological features, and the potential therapeutic perspectives related therewith. At the central level, they have been shown to be strongly involved in several functions, including memory processes [63–68] and the regulation of food intake [69,70]. More interestingly, in the context of the present review, a single study conducted in the 1990s reported that preferential 5-HT_4 agonists, such as renzapride, seemed to be able to facilitate the release of 5-HT within the hippocampal area [71]. It is noteworthy that these experiments, initially conducted to better understand the mechanisms underlying the effect of some anxiolytic drugs [72], brought the first clue of a putative role played by 5-HT_4 receptors in AD therapy.

As explained in detail earlier, the possibility to acutely, directly enhance central 5-HT outflow with a given class of compounds resulted in promising possibilities for the development of new ADs, which could display a more rapid onset of action than SSRIs and other 'indirect' agents. First, we decided to assess the ability of selective 5-HT_4 pharmacological agents to influence 5-HT neuronal impulse flow, measured using single-cell extracellular recordings. When acutely administered, 5-HT_4 agonists, such as cisapride or prucalopride, are able to enhance the firing rate of a subpopulation of responding DR 5-HT neurons ('responders'), which represent approximately 45% of the whole [73]. We also observed that prucalopride counteracts the inhibitory effect of acute SSRIs on DR responders [74]. The 5-HT_4-dependent control was then assessed in a more global manner, by performing successive recording tracks ('descents') along the DR to draw a picture of the average 5-HT neuronal firing rate. Both prucaloride and RS 67333, another selective 5-HT_4 agonist, enhanced the mean activity of 5-HT neurons when administered 30 min before starting the descents [75]. This effect was fully blocked by an acute injection of the selective 5-HT_4 antagonist GR 125487 [75]. More importantly, it was also present at very similar levels after chronic administration of each drug for either 3 or 21 days [75]. Consistent with these findings, the mean firing rate of DR 5-HT neurons was found to be reduced by more than 50% in 5-HT_4 knockout mice, with respect to their wild-type littermates [76]. Also, and similarly to the acute conditions, the continuous co-administration of either prucalopride or RS 67333 with the SSRI citalopram during 3 days increased 5-HT neuron activity, with an amplitude very similar to that observed when each 5-HT_4 agonist was given alone [74].

The aforementioned positive influence exerted by 5-HT_4 receptors on central 5-HT neuron activity was paralleled by the apparition of various biological markers within the brain, occurring typically after chronic AD administration, and postsynaptically reflecting an increased 5-HT transmission. Thus, after 3 days of chronic administration, RS 67333 and/or prucalopride were already able to induce the manifestation of a 5-HT_{1A}-mediated inhibitory tone on hippocampal pyramidal neurons, an increased phosphorylation of CREB and an enhancement of adult mitogenesis within this region [77]. In agreement with our results, the same regimen (using RS 67333) has recently been reported to increase 5-HT release in the ventral hippocampus [78]. The 5-HT_4 partial agonist SL 65.0155 has also been shown to facilitate CREB phosphorylation after three subchronic administrations, performed within a 24-h timeframe [79]. By contrast, classical ADs such as SSRIs produce similar postsynaptic effects after only 2 or 3 weeks when given alone [8–11,80–83]. Interestingly, in line with our previous findings, 3 days of combined treatment of the SSRI citalopram with either prucalopride or RS 67333 augmented both the inhibitory tonus exerted by endogenous 5-HT on hippocampal 5-HT_{1A} receptors, and the phosphorylation of CREB, with a much higher amplitude than what was observed with each 5-HT_4 agonist on its own [74]. In addition, a 3-day treatment with RS 67333 proved effective in alleviating the syndromes thought to reflect 'depression' in the olfactory bulbectomy and chronic mild stress behavioral tests. In the first one, RS 67333 reduces the hyperactivity of olfactory bulbectomy rats when exposed to a stressful (hyperilluminated) environment, with the same amplitude as is observed after 14 days of citalopram [77]. A very similar difference in the respective kinetics of RS 67333 and citalopram is observed concerning their ability to reverse the chronic mild stress-induced anhedonia, measured by sucrose consumption [77]. It appears, therefore, that 5-HT_4 agonists are able to trigger AD-like effects at least four- to seven-times more rapidly than classical molecules do in numerous experimental models [77]. Clinical trials have yet to be conducted with such compounds; interestingly, both animal [84,85] and human [86] post-mortem

studies revealed important changes of 5-HT$_4$ receptor expression in (pseudo)depressed subjects. In addition, a recent report has shown that the p11 protein is apparently required for the expression of some behavioral AD-like actions elicited by 5-HT$_4$ receptor stimulation [87]. In addition, both proteins are co-expressed in brain regions relevant for depression, and p11 increases surface expression of the 5-HT$_4$ receptor and facilitates its intracellular signaling [87]. However, anatomical data indicate that both 5-HT$_4$ mRNA and protein are poorly expressed within the rat DR [88,89], with 5-HT cell bodies being virtually devoid of these receptors [88]. Therefore, it appears unlikely that such a weak distribution could account for the effects described earlier. In the rodent brain, the most 5-HT$_4$-enriched areas are found in the basal ganglia, especially along the nigrostriatal and mesoaccumbal dopaminergic pathways, and in limbic areas such as the olfactory tubercles and the hippocampus [89–91]. Although the levels were reported to be moderate in the cortical mantle [89,90], a more detailed examination of the available figures revealed that the mPFC (both infralimbic and prelimbic subregions) expressed substantially more 5-HT$_4$ mRNA and protein than other cortical areas [91], a feature also displayed by the human brain [92]. Furthermore, it had already been reported that the electrical stimulation of the mPFC facilitated the activity of 40–45% of DR 5-HT cell bodies [21]. This proportion was strikingly close to what we observed concerning 'responding' 5-HT neurons [73]. In addition, an inhibitory, 5-HT$_{1A}$-mediated, 'long-loop feedback' originating from the mPFC has been demonstrated, and was thought to concern approximately half of DR 5-HT neurons [93]. Finally, there was evidence suggesting that 5-HT$_{1A}$ and 5-HT$_4$ receptors are mostly co-localized within the same pyramidal neurons in the mPFC [94]. Altogether, these data favored the possibility that the 5-HT$_4$-dependent facilitatory control also originates from the mPFC. To confirm this hypothesis, we used herpes simplex virus particles, transformed to induce an overexpression of 5-HT$_4$ receptors in discrete brain areas. In a particularly striking manner, the microinfusion of viral particles into the mPFC induced a marked increase of DR 5-HT neuron firing rate [75]. Conversely, it had no effect when administered in the striatum, the hippocampus or the olfactory bulbs [75], three brain areas being among those which constitutively display the highest 5-HT$_4$ receptor expression (see earlier). Interestingly, recent data indicate that, in contrast to what is seen in the striatum and hippocampus, 5-HT$_4$ receptor binding is not downregulated in the mPFC after 21 days of treatment with the SSRI fluoxetine [95]. This result adds further support to the idea that the mPFC constitutes a major site of origin of the 5-HT$_4$-mediated positive control on 5-HT neuron activity, considering that this control also is not desensitized by long-term (21 days) administration of a 5-HT$_4$ agonist [75]. We propose that the stimulation of 5-HT$_4$ receptors within the mPFC triggers a positive, 'long-loop feedback' on DRN 5-HT function **(Figure 1)**. According to this model, the projections connecting the mPFC to the DRN, and using glutamatergic neurotransmission, would constitute the vector of the feedback.

5-HT$_7$ receptor antagonists: a possible role for mPFC glial cells

5-HT$_7$ receptors constitute another 5-HT receptor subtype that has recently received attention as a new target for the development of fast-acting ADs. These receptors are the latest identified members of the 5-HT receptor family and have been found to activate adenylate cyclase [96–100]. Earlier studies have suggested that the therapeutic action of ADs might be mediated, at least in part, by 5-HT$_7$ receptors. Thus, chronic treatment with AD drugs led to a downregulation of these receptors in the hypothalamus [101,102] and to a reduction of the effectiveness of their activation within the rat hippocampus [103]. Conversely, several atypical antipsychotics, such as amisulpride, risperidone, olanzapine or aripiprazole, which possess antagonistic properties for the 5-HT$_7$ receptors [98,104–106], have therapeutic indications as an adjunctive treatment for depression [107–113]. In particular, recent studies have demonstrated that the AD actions of amisulpride and aripiprazole require 5-HT$_7$ receptors, because these agents had no AD-like effect in 5-HT$_7$ receptor knockout mice compared with what was seen in their wild-type littermates [114,115]. More direct evidence of the involvement of 5-HT$_7$ receptors in AD responses was provided by studies showing that pharmacological blockade of 5-HT$_7$ receptors, using the potent and selective 5-HT$_7$ receptor antagonist SB-269970 [116–118], or inactivation of the 5-HT$_7$ receptor gene, produces AD-like effects in behavioral rodent models [119–123]. In addition, similarly to SSRIs, the blockade or

inactivation of the 5-HT$_7$ receptors affect sleep parameters in a pattern opposite to that seen in depressed patients [121,124]. Finally, it has been reported that SB-269970 potentiated both the effects of several ADs, and the rapid eye movement sleep suppression induced by the SSRI citalopram [123,125,126], suggesting that blockade of 5-HT$_7$ receptors may facilitate the actions of AD treatments. In keeping with this hypothesis, we recently reported that 5-HT$_7$ antagonism prevents the suppressant effect of SSRIs on DR 5-HT neuron electrical activity [119].

More interestingly, there is recent evidence suggesting that the AD properties of 5-HT$_7$ receptor antagonists may rise with a faster onset of action than classical compounds. As outlined previously, all ADs have been demonstrated to promote hippocampal neurogenesis and, in turn, such a cellular plasticity seems to be essential for the achievement of an AD response [127–129]. Whereas cell proliferation in the rat hippocampus is enhanced after 2–3 weeks of treatment with classical molecules [11,130], a 1-week treatment with the 5-HT$_7$ receptor antagonist SB-269970 was sufficient to increase this same parameter [119]. Also in support of a faster AD-like profile of 5-HT$_7$ receptor antagonists, we reported that a 1-week treatment with SB-269970 fails to modify the firing activity of DR 5-HT neurons, but desensitizes the inhibitory action of 5-HT$_{1A}$ autoreceptors [119]. By contrast, a similar reduced 5-HT$_{1A}$ receptor responsiveness takes place only after 2–3 weeks of treatment with other ADs [131–133]. In addition, our recent data showing that SB-269970 counteracted the depressive-like behavior in olfactory bulbectomized rats after a 7-day treatment, while fluoxetine remained ineffective within the same timeframe [119], further supports the hypothesis that 5-HT$_7$ receptor antagonists may act with a more rapid onset of action. The precise mechanism underlying the AD-like effects of 5-HT$_7$ receptor antagonism is presently not known. Our electrophysiological data give direct evidence of a negative control exerted by 5-HT$_7$ receptors on 5-HT neuron activity. Thus, the systemic administration of the potent and selective 5-HT$_7$ receptor agonist AS-19 [134] inhibited the firing rate of DR 5-HT neurons in anesthetized rats, an effect prevented by prior systemic injection of SB-26970 [119]. This inhibitory control seems to be indirect. Indeed, biochemical studies performed on midbrain slices suggest that 5-HT$_7$ receptors are not located on 5-HT-containing neurons in the DR [135,136]. Interestingly, microdialysis studies have found that SB-269970 enhanced the release of 5-HT induced by citalopram within the mPFC, suggesting that this region could be implicated in the aforementioned synergic interaction between 5-HT$_7$ receptor antagonists and ADs [125]. In support of this hypothesis, functional 5-HT$_7$ receptors, positively coupled to adenylyl cyclase, have been identified in cultured astrocytes derived from the rat cortex [137,138]. Furthermore, a continuous (3 day) exposure to the ADs mianserin or amitriptyline enhanced 5-HT$_7$ receptor-mediated adenylyl cyclase activation of cortical astrocytes [138]. Considering the recently evidenced importance of mPFC glia on the effects of ADs [59], and the fact that mPFC astrocytes are directly activated by SSRIs ADs [139], 5-HT$_7$ receptor antagonists might, therefore, act via a glia-mediated modulation of the cortico-DR transmission to exert their AD-like influence. Indeed, it has been shown from single cell real-time PCR studies that 5-HT$_7$ receptors are not directly expressed by glutamatergic pyramidal neurons within the mPFC [94]. This latter data caused us to propose the alternative hypothesis that 5-HT$_7$ receptors localized in GABAergic interneurons of the mPFC (and/or of the DR) may also contribute to the aforementioned effects [97]. The possible mechanisms discussed earlier are summarized in **Figure 1**; whatever the exact cellular localization of the mPFC 5-HT$_7$ receptors involved, we hypothesize that their blockade induces an enhanced release of glutamate in the DR, which in turn increases 5-HT neuron activity.

Conclusion & future perspective

The data presented earlier confirm that it is actually possible to obtain faster AD responses than what has been achieved using standard molecules. They also point out that current pharmacological approaches have not reached their maximum efficacy/onset of action, and that the supposedly incompressible long delay of action related to monoaminergic drug treatment is not an immutable dogma. Therefore, the connection existing between the mPFC and DR 5-HT neurons appear to constitute a critical vector to develop new AD strategies. The glutamatergic neurotransmission stemming from mPFC pyramidal neurons can apparently act as a potent motor to boost central 5-HT function, whether it is triggered by a direct electrical stimulation or by a pharmacological one **(Figure 1)**. It seems that the function of this motor

is particularly dependent on the 'fueling' properties of the glial system, to the extent that manipulating the mPFC glia results in tangible effects on depression-related behaviors. Several studies have pointed out that the blockade of some types of glutamate receptors, such as NMDA receptors, can also produce very fast AD-like effects. These effects appear to be related to the existence of a complex network within the mPFC itself, involving inhibitory interneurons and/or reciprocal collaterals, which regulate the activity of pyramidal cells [140]. Interestingly, the fast AD-like effects of the NMDA antagonist ketamine are paralleled by a significant increase of synaptogenesis within the mPFC [140]; it is tempting to speculate that this enhanced connectivity may improve the excitability of pyramidal neurons, resulting, again, in an increased release of glutamate in the vicinity of 5-HT cell bodies. Moreover, these very results demonstrate that, at least within the mPFC, morphological changes can be achieved within a very rapid time-frame by using pharmacological tools. They therefore contribute to re-establish a connection between two concepts in the field of 'fast AD' research. Should indeed the tools be of viral, molecular, pharmacological, electrical or even magnetic nature, as the increasing use of repetitive transcranial magnetic stimulation in the field of depression already gives a glimpse of, modulating the activity of the descending mPFC-DR pathway will likely constitute a major strategy to develop new fast-acting AD treatments in the near future.

Disclosure

L Lambás-Señas, N Haddjeri and G Lucas are employees of INSERM.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Duman RS: A silver bullet for the treatment of depression? *Neuron* 55(5), 679–681 (2007).

2 Souery D, Papakostas GI, Trivedi MH: Treatment-resistant depression. *J. Clin. Psychiatry* 67(Suppl. 6), 16–22 (2006).

3 Machado-Vieira R, Salvadore G, Luckenbaugh DA, Manji HK, Zarate CA: Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depressive disorder. *J. Clin. Psychiatry* 69(6), 946–958 (2008).

4 Michelsen KA, Schmitz C, Steinbusch HWM: The dorsal raphe nucleus – from silver stainings to a role in depression. *Brain Res. Rev.* 55(2), 329–342 (2007).

5 Blier P, de Montigny C: Serotonin and drug-induced therapeutic responses in major depression, obsessive–compulsive and panic disorders. *Neuropsychopharmacology* 21(Suppl. 2), 91S–98S (1999).

6 Szabo ST, Blier P: Effects of the selective norepinephrine reuptake inhibitor reboxetine on norepinephrine and serotonin transmission in the rat hippocampus. *Neuropsychopharmacology* 25(6), 845–857 (2001).

7 Artigas F, Nutt DJ, Shelton R: Mechanism of action of antidepressants. *Psychopharmacol. Bull.* 36(Suppl. 2), 123–132 (2002).

8 Duman RS, Nakagawa S, Malberg J: Regulation of adult neurogenesis by antidepressant treatment. *Neuropsychopharmacology* 25(6), 836–844 (2001).

9 Nestler EJ, Barrot M, DiLeone RJ *et al.*: Neurobiology of depression. *Neuron* 34(1), 13–25 (2002).

10 Thome J, Sakai N, Shin K *et al.*: cAMP response element-mediated gene transcription is upregulated by chronic antidepressant treatment. *J. Neurosci.* 20(11), 4030–4036 (2000).

11 Malberg JE, Eisch AJ, Nestler EJ, Duman RS: Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J. Neurosci.* 20(24), 9104–9110 (2000).

▪ **First full demonstration of an enhanced hippocampal mitogenesis following antidepressant treatment.**

12 Castrén E, Võikar V, Rantamäki T: Role of neurotrophic factors in depression. *Curr. Opin. Pharmacol.* 7(1), 18–21 (2007).

13 Hunsberger JG, Newton SS, Bennett AH *et al.*: Antidepressant actions of the exercise-regulated gene *VGF*. *Nat. Med.* 13(12), 1476–1482 (2007).

14 Thakker-Varia S, Krol JJ, Nettleton J *et al.*: The neuropeptide VGF produces antidepressant-like behavioral effects and enhances proliferation in the hippocampus. *J. Neurosci.* 27(45), 12156–12167 (2007).

15 Duric V, Banasr M, Licznerski P *et al.*: A negative regulator of MAP kinase causes depressive behavior. *Nat. Med.* 16(11), 1328–1332 (2010).

16 Alexander B, Warner-Schmidt J, Eriksson T *et al.*: Reversal of depressed behaviors in mice by *p11* gene therapy in the nucleus accumbens. *Sci. Transl. Med.* 2(54), 54ra76 (2010).

17 Svenningsson P, Chergui K, Rachleff I *et al.*: Alterations in 5-HT_{1B} receptor function by p11 in depression-like states. *Science* 311(5757), 77–80 (2006).

18 Hammen C. Stress and depression. *Ann. Rev. Clin. Psychol.* 1, 293–319 (2005).

19 Chen G, Twyman R, Manji HK: p11 and gene therapy for severe psychiatric disorders: a practical goal? *Sci. Transl. Med.* 2(54), 54ps51 (2010).

20 Manji HK, Duman RS: Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. *Psychopharmacol. Bull.* 35(2), 5–49 (2001).

21 Celada P, Puig MV, Casanovas JM, Guillazo G, Artigas F: Control of dorsal raphe serotonergic neurons by the medial prefrontal cortex: involvement of serotonin-1A, GABA(A), and glutamate receptors. *J. Neurosci*. 21(24), 9917–9929 (2001).

■■ **Reports on the complex relationship existing between glutamatergic efferents from the medial prefrontal cortex (mPFC), and midbrain serotonin (5-HT) neurons.**

22 Hajós M, Hajós-Korcsok E, Sharp T: Role of the medial prefrontal cortex in 5-HT_{1A} receptor-induced inhibition of 5-HT neuronal activity in the rat. *Br. J. Pharmacol*. 126(8), 1741–1750 (1999).

23 Celada P, Puig M, Amargós-Bosch M, Adell A, Artigas F: The therapeutic role of 5-HT_{1A} and 5-HT_{2A} receptors in depression. *J. Psychiatry Neurosci*. 29(4), 252–265 (2004).

24 Bridges PK, Bartlett JR, Hale AS *et al.*: Psychosurgery: stereotactic subcaudate tractomy. An indispensable treatment. *Br. J. Psychiatry* 165(5), 599–611; discussion 612–613 (1994).

25 Hodgkiss AD, Malizia AL, Bartlett JR, Bridges PK: Outcome after the psychosurgical operation of stereotactic subcaudate tractotomy, 1979–1991. *J. Neuropsychiatry Clin. Neurosci*. 7(2), 230–234 (1995).

26 Abosch A, Cosgrove GR: Biological basis for the surgical treatment of depression. *Neurosurg. Focus* 25(1), E2 (2008)

27 Andrade P, Noblesse LHM, Temel Y *et al.*: Neurostimulatory and ablative treatment options in major depressive disorder: a systematic review. *Acta Neurochir. (Wien)* 152(4), 565–577 (2010).

28 Mashour GA, Walker EE, Martuza RL: Psychosurgery: past, present, and future. *Brain Res. Brain Res. Rev*. 48(3), 409–419 (2005).

29 Kim M, Lee T, Choi C: Review of long-term results of stereotactic psychosurgery. *Neurol. Med. Chir. (Tokyo)* 42(9), 365–371 (2002).

30 Drevets WC, Bogers W, Raichle ME: Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur. Neuropsychopharmacol*. 12(6), 527–544 (2002).

31 Mayberg HS: Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. *Br. Med. Bull*. 65, 193–207 (2003).

32 Kennedy SH, Konarski JZ, Segal ZV *et al.*: Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *Am. J. Psychiatry* 164(5), 778–788 (2007).

33 Mayberg HS: Modulating limbic-cortical circuits in depression: targets of antidepressant treatments. *Semin. Clin. Neuropsychiatry* 7(4), 255–268 (2002).

34 Kennedy SH, Evans KR, Krüger S *et al.*: Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *Am. J. Psychiatry* 158(6), 899–905 (2001).

35 Mayberg HS: Positron emission tomography imaging in depression: a neural systems perspective. *Neuroimaging Clin. N. Am*. 13(4), 805–815 (2003).

36 Seminowicz DA, Mayberg HS, McIntosh AR *et al.*: Limbic-frontal circuitry in major depression: a path modeling metanalysis. *Neuroimage* 22(1), 409–418 (2004).

37 George MS, Ketter TA, Parekh PI *et al.*: Brain activity during transient sadness and happiness in healthy women. *Am. J. Psychiatry* 152(3), 341–351 (1995).

38 Mayberg HS, Liotti M, Brannan SK *et al.*: Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am. J. Psychiatry* 156(5), 675–682 (1999).

39 Dougherty DD, Weiss AP, Cosgrove GR *et al.*: Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression. *J. Neurosurg.* 99(6), 1010–1017 (2003).

40 Mayberg HS, Brannan SK, Mahurin RK *et al.*: Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 8(4), 1057–1061 (1997).

41 Mayberg HS, Brannan SK, Tekell JL *et al.*: Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol. Psychiatry* 48(8), 830–843 (2000).

42 Nobler MS, Oquendo MA, Kegeles LS *et al.*: Decreased regional brain metabolism after ECT. *Am. J. Psychiatry* 158(2), 305–308 (2001).

43 Mottaghy FM, Keller CE, Gangitano M *et al.*: Correlation of cerebral blood flow and treatment effects of repetitive transcranial magnetic stimulation in depressed patients. *Psychiatry Res*. 115(1–2), 1–14 (2002).

44 Mayberg HS, Lozano AM, Voon V *et al.*: Deep brain stimulation for treatment-resistant depression. *Neuron* 45(5), 651–660 (2005).

■■ **First demonstration of a clinical efficacy for deep-brain stimulation (DBS) in depressed patients.**

45 Lozano AM, Mayberg HS, Giacobbe P *et al.*: Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biol. Psychiatry* 64(6), 461–467 (2008).

46 McNeely HE, Mayberg HS, Lozano AM, Kennedy SH: Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. *J. Nerv. Ment. Dis*. 196(5), 405–410 (2008).

■ **Confirmation of DBS efficacy in a greater number of patients.**

47 Beurrier C, Bioulac B, Audin J, Hammond C: High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. *J. Neurophysiol*. 85(4), 1351–1356 (2001).

48 Breit S, Schulz JB, Benabid A: Deep brain stimulation. *Cell Tissue Res*. 318(1), 275–288 (2004).

49 Shin DS, Samoilova M, Cotic M *et al.*: High frequency stimulation or elevated K^+ depresses neuronal activity in the rat entopeduncular nucleus. *Neuroscience* 149(1), 68–86 (2007).

50 Hamani C, Diwan M, Macedo CE *et al.*: Antidepressant-like effects of medial prefrontal cortex deep brain stimulation in rats. *Biol. Psychiatry* 67(2), 117–124 (2010).

■■ **Study of DBS effects in rodent brain. Demonstration that 5-HT plays a pivotal role in its behavioral expression.**

51 Neafsey EJ, Terreberry RR, Hurley KM, Ruit KG, Frystak RJ: Anterior cingulated cortex in rodents: connections, visceral control functions, and implications for emotion. In: *Neurobiology of the Cingulated Cortex and Limbic Thalamus*: *A Comprehensive Handbook*. Vogt BA, Gabriel M (Eds). Birkhauser, Berlin, Germany, 216–223 (1993).

52 Juckel G, Mendlin A, Jacobs BL: Electrical stimulation of rat medial prefrontal cortex enhances forebrain serotonin output: implications for electroconvulsive therapy and transcranial magnetic stimulation in depression. *Neuropsychopharmacology* 21(3), 391–398 (1999).

53 Karreman M, Moghaddam B: The prefrontal cortex regulates the basal release of dopamine in the limbic striatum: an effect mediated by ventral tegmental area. *J. Neurochem*. 66(2), 589–598 (1996).

54 Rossetti ZL, Marcangione C, Wise RA: Increase of extracellular glutamate and expression of Fos-like immunoreactivity in the ventral tegmental area in response to electrical stimulation of the prefrontal cortex. *J. Neurochem*. 70(4), 1503–1512 (1998).

55 Taber MT, Das S, Fibiger HC: Cortical regulation of subcortical dopamine release: mediation via the ventral tegmental area. *J. Neurochem*. 65(3), 1407–1410 (1995).

56 Etievant A, Oosterhof CA, Bétry C *et al.*: Effect of medial prefrontal cortex deep brain stimulation on dorsal raphe 5-HT neuronal activity and hippocampal metaplasticity. Presented at: *40th Annual Meeting of Society for Neurosciences*. San Diego, CA, USA, 13–17 November 2010.

57 Peyron C, Petit JM, Rampon C, Jouvet M, Luppi PH: Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. *Neuroscience* 82(2), 443–468 (1998).

■ **A very complete anatomical study, describing the dense innervation projecting from the mPFC toward dorsal raphé 5-HT neurons.**

58 Takagishi M, Chiba T: Efferent projections of the infralimbic (area 25) region of the medial prefrontal cortex in the rat: an anterograde tracer PHA-L study. *Brain Res*. 566(1–2), 26–39 (1991).

59 Banasr M, Duman RS: Glial loss in the prefrontal cortex is sufficient to induce depressive-like behaviors. *Biol. Psychiatry* 64(10), 863–870 (2008).

■■ **Evidence that the glial system within the mPFC plays an important role in mood control and expression.**

60 Banasr M, Rothstein JD, Tanaka K, Duman RS, Sanacora G: Role of glial glutamate transporters GLT1 (EEAT2) in the antidepressant action of Riluzole and Ceftriaxone. Presented at: *65th Annual Meeting of Society of Biological Psychiatry*. New Orleans, LA, USA, 20–22 May 2010.

61 Dumuis A, Bouhelal R, Sebben M, Bockaert J: A 5-HT receptor in the central nervous system, positively coupled with adenylate cyclase, is antagonized by ICS 205 930. *Eur. J. Pharmacol*. 146(1), 187–188 (1988).

62 Dumuis A, Bouhelal R, Sebben M, Cory R, Bockaert J: A nonclassical 5-hydroxytryptamine receptor positively coupled with adenylate cyclase in the central nervous system. *Mol. Pharmacol*. 34(6), 880–887 (1988).

63 Bockaert J, Claeysen S, Compan V, Dumuis A: 5-HT_4 receptors. *Curr. Drug Targets CNS Neurol. Disord*. 3(1), 39–51 (2004).

64 Letty S, Child R, Dumuis A *et al.*: 5-HT_4 receptors improve social olfactory memory in the rat. *Neuropharmacology* 36(4–5), 681–687 (1997).

65 Levallet G, Hotte M, Boulouard M, Dauphin F: Increased particulate phosphodiesterase 4 in the prefrontal cortex supports 5-HT_4 receptor-induced improvement of object recognition memory in the rat. *Psychopharmacology (Berl.)* 202(1–3), 125–139 (2009).

66 Mohler EG, Shacham S, Noiman S *et al.*: VRX-03011, a novel 5-HT_4 agonist, enhances memory and hippocampal acetylcholine efflux. *Neuropharmacology* 53(4), 563–573 (2007).

67 Moser PC, Bergis OE, Jegham S *et al.*: SL65.0155, a novel 5-hydroxytryptamine(4) receptor partial agonist with potent cognition-enhancing properties. *J. Pharmacol. Exp. Ther*. 302(2), 731–741 (2002).

68 Orsetti M, Dellarole A, Ferri S, Ghi P: Acquisition, retention, and recall of memory after injection of RS67333, a 5-HT(4) receptor agonist, into the nucleus basalis magnocellularis of the rat. *Learn. Mem*. 10(5), 420–426 (2003).

69 Compan V, Zhou M, Grailhe R *et al.*: Attenuated response to stress and novelty and hypersensitivity to seizures in 5-HT_4 receptor knockout mice. *J. Neurosci*. 24(2), 412–419 (2004).

70 Jean A, Conductier G, Manrique C *et al.*: Anorexia induced by activation of serotonin 5-HT_4 receptors is mediated by increases in CART in the nucleus accumbens. *Proc. Natl Acad. Sci. USA* 104(41), 16335–16340 (2007).

71 Ge J, Barnes NM: 5-HT_4 receptor-mediated modulation of 5-HT release in the rat hippocampus *in vivo*. *Br. J. Pharmacol*. 117(7), 1475–1480 (1996).

72 Barnes NM, Cheng CH, Costall B, Ge J, Naylor RJ: Differential modulation of extracellular levels of 5-hydroxytryptamine in the rat frontal cortex by (R)- and (S)-zacopride. *Br. J. Pharmacol*. 107(1), 233–239 (1992).

73 Lucas G, Debonnel G: 5-HT_4 receptors exert a frequency-related facilitatory control on dorsal raphé nucleus 5-HT neuronal activity. *Eur. J. Neurosci*. 16(5), 817–822 (2002).

74 Lucas G, Du J, Romeas T *et al.*: Selective serotonin reuptake inhibitors potentiate the rapid antidepressant-like effects of serotonin 4 receptor agonists in the rat. *PLoS One* 5(2), e9253 (2010).

75 Lucas G, Compan V, Charnay Y *et al.*: Frontocortical 5-HT_4 receptors exert positive feedback on serotonergic activity: viral transfections, subacute and chronic treatments with 5-HT_4 agonists. *Biol. Psychiatry* 57(8), 918–925 (2005).

76 Conductier G, Dusticier N, Lucas G *et al.*: Adaptive changes in serotonin neurons of the raphe nuclei in 5-HT_4 receptor knockout mouse. *Eur. J. Neurosci*. 24(4), 1053–1062 (2006).

77 Lucas G, Rymar VV, Du J *et al.*: Serotonin$_4$ (5-HT_4) receptor agonists are putative antidepressants with a rapid onset of action. *Neuron* 55(5), 712–725 (2007).

■ **First demonstration that 5-HT_4 agonists may be used as a novel class of antidepressants, with a four- to seven-fold more rapid onset of action than standard molecules.**

78 Licht CL, Knudsen GM, Sharp T: Effects of the 5-HT(4) receptor agonist RS67333 and paroxetine on hippocampal extracellular 5-HT levels. *Neurosci. Lett*. 476(2), 58–61 (2010).

79 Tamburella A, Micale V, Navarria A, Drago F: Antidepressant properties of the 5-HT_4 receptor partial agonist, SL65.0155: behavioral and neurochemical studies in rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 33(7), 1205–1210 (2009).

80 Besson A, Haddjeri N, Blier P, de Montigny C: Effects of the co-administration of mirtazapine and paroxetine on serotonergic neurotransmission in the rat brain. *Eur. Neuropsychopharmacol*. 10(3), 177–188 (2000).

81 Haddjeri N, Blier P, de Montigny C: Long-term antidepressant treatments result in a tonic activation of forebrain 5-HT_{1A} receptors. *J. Neurosci*. 18(23), 10150–10156 (1998).

82 Nibuya M, Nestler EJ, Duman RS: Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J. Neurosci*. 16(7), 2365–2372 (1996).

83 Tiraboschi E, Tardito D, Kasahara J *et al.*: Selective phosphorylation of nuclear CREB by fluoxetine is linked to activation of CaM kinase IV and MAP kinase cascades. *Neuropsychopharmacology* 29(10), 1831–1840 (2004).

84 Licht CL, Marcussen AB, Wegener G *et al.*: The brain 5-HT_4 receptor binding is down-regulated in the Flinders Sensitive Line depression model and in response to paroxetine administration. *J. Neurochem*. 109(5), 1363–1374 (2009).

85 Licht CL, Kirkegaard L, Zueger M *et al.*: Changes in 5-HT_4 receptor and 5-HT transporter binding in olfactory bulbectomized and glucocorticoid receptor heterozygous mice. *Neurochem. Int.* 56(4), 603–610 (2010).

86 Rosel P, Arranz B, Urretavizcaya M *et al.*: Altered 5-HT_{2A} and 5-HT_4 postsynaptic receptors and their intracellular signalling systems IP3 and cAMP in brains from depressed violent suicide victims. *Neuropsychobiology* 49(4), 189–195 (2004).

87 Warner-Schmidt JL, Flajolet M, Maller A *et al.*: Role of p11 in cellular and behavioral effects of 5-HT_4 receptor stimulation. *J. Neurosci.* 29(6), 1937–1946 (2009).

88 Vilaró MT, Cortés R, Gerald C *et al.*: Localization of 5-HT_4 receptor mRNA in rat brain by *in situ* hybridization histochemistry. *Brain Res. Mol. Brain Res.* 43(1–2), 356–360 (1996).

89 Waeber C, Sebben M, Nieoullon A, Bockaert J, Dumuis A: Regional distribution and ontogeny of 5-HT_4 binding sites in rodent brain. *Neuropharmacology* 33(3–4), 527–541 (1994).

90 Grossman CJ, Kilpatrick GJ, Bunce KT: Development of a radioligand binding assay for 5-HT_4 receptors in guinea-pig and rat brain. *Br. J. Pharmacol.* 109(3), 618–624 (1993).

91 Vilaró MT, Cortés R, Mengod G: Serotonin 5-HT_4 receptors and their mRNAs in rat and guinea pig brain: distribution and effects of neurotoxic lesions. *J. Comp. Neurol.* 484(4), 418–439 (2005).

92 Bonaventure P, Hall H, Gommeren W *et al.*: Mapping of serotonin 5-HT(4) receptor mRNA and ligand binding sites in the post-mortem human brain. *Synapse* 36(1), 35–46 (2000).

93 Martín-Ruiz R, Ugedo L: Electrophysiological evidence for postsynaptic 5-HT(1A) receptor control of dorsal raphe 5-HT neurones. *Neuropharmacology* 41(1), 72–78 (2001).

94 Feng J, Cai X, Zhao J, Yan Z: Serotonin receptors modulate GABA(A) receptor channels through activation of anchored protein kinase C in prefrontal cortical neurons. *J. Neurosci.* 21(17), 6502–6511 (2001).

95 Vidal R, Valdizán EM, Mostany R, Pazos A, Castro E: Long-term treatment with fluoxetine induces desensitization of 5-HT_4 receptor-dependent signalling and functionality in rat brain. *J. Neurochem.* 110(3), 1120–1127 (2009).

96 Hedlund PB, Sutcliffe JG: Functional, molecular and pharmacological advances in 5-HT_7 receptor research. *Trends Pharmacol. Sci.* 25(9), 481–486 (2004).

97 Mnie-Filali O, Lambás-Señas L, Zimmer L, Haddjeri N: 5-HT_7 receptor antagonists as a new class of antidepressants. *Drug News Perspect.* 20(10), 613–618 (2007).

98 Mnie-Filali O, Lambas-Señas L, Scarna H, Haddjeri N: Therapeutic potential of 5-HT_7 receptors in mood disorders. *Curr. Drug Targets* 10(11), 1109–1117 (2009).

99 Nandam LS, Jhaveri D, Bartlett P: 5-HT_7, neurogenesis and antidepressants: a promising therapeutic axis for treating depression. *Clin. Exp. Pharmacol. Physiol.* 34(5–6), 546–551 (2007).

100 Ruat M, Traiffort E, Leurs R *et al.*: Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-HT_7) activating cAMP formation. *Proc. Natl Acad. Sci. USA* 90(18), 8547–8551 (1993).

101 Mullins UL, Gianutsos G, Eison AS: Effects of antidepressants on 5-HT_7 receptor regulation in the rat hypothalamus. *Neuropsychopharmacology* 21(3), 352–367 (1999).

102 Sleight AJ, Carolo C, Petit N, Zwingelstein C, Bourson A: Identification of 5-hydroxytryptamine$_7$ receptor binding sites in rat hypothalamus: sensitivity to chronic antidepressant treatment. *Mol. Pharmacol.* 47(1), 99–103 (1995).

103 Tokarski K, Zahorodna A, Bobula B *et al.*: Repeated administration of citalopram and imipramine alters the responsiveness of rat hippocampal circuitry to the activation of 5-HT_7 receptors. *Eur. J. Pharmacol.* 524(1–3), 60–66 (2005).

104 Chivers JK, Gommeren W, Leysen JE, Jenner P, Marsden CD: Comparison of the *in vitro* receptor selectivity of substituted benzamide drugs for brain neurotransmitter receptors. *J. Pharm. Pharmacol.* 40(6), 415–421 (1988).

105 Roth BL, Craigo SC, Choudhary MS *et al.*: Binding of typical and atypical antipsychotic agents to 5-hydroxytryptamine-6 and 5-hydroxytryptamine-7 receptors. *J. Pharmacol. Exp. Ther.* 268(3), 1403–1410 (1994).

106 Thomas DR, Gittins SA, Collin LL *et al.*: Functional characterisation of the human cloned 5-HT_7 receptor (long form); antagonist profile of SB-258719. *Br. J. Pharmacol.* 124(6), 1300–1306 (1998).

107 Barbee JG, Conrad EJ, Jamhour NJ: The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. *J. Clin. Psychiatry* 65(7), 975–981 (2004).

108 Berman RM, Marcus RN, Swanink R *et al.*: The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J. Clin. Psychiatry* 68(6), 843–853 (2007).

109 Hardoy MC, Carta MG: Strategy to accelerate or augment the antidepressant response and for an early onset of SSRI Activity. Adjunctive amisulpride to fluvoxamine in major depressive disorder. *Clin. Pract. Epidemiol. Ment. Health* 6, 1–3 (2010).

110 Hirose S, Ashby CR: An open pilot study combining risperidone and a selective serotonin reuptake inhibitor as initial antidepressant therapy. *J. Clin. Psychiatry* 63(8), 733–736 (2002).

111 Nelson JC, Pikalov A, Berman RM: Augmentation treatment in major depressive disorder: focus on aripiprazole. *Neuropsychiatr. Dis. Treat.* 4(5), 937–948 (2008).

112 Ostroff RB, Nelson JC: Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *J. Clin. Psychiatry* 60(4), 256–259 (1999).

113 Shelton RC, Tollefson GD, Tohen M *et al.*: A novel augmentation strategy for treating resistant major depression. *Am. J. Psychiatry* 158(1), 131–134 (2001).

114 Abbas AI, Hedlund PB, Huang X *et al.*: Amisulpride is a potent 5-HT_7 antagonist: relevance for antidepressant actions *in vivo*. *Psychopharmacology (Berl.)* 205(1), 119–128 (2009).

115 Sarkisyan G, Roberts AJ, Hedlund PB: The 5-HT_7 receptor as a mediator and modulator of antidepressant-like behavior. *Behav. Brain Res.* 209(1), 99–108 (2010).

116 Hagan JJ, Price GW, Jeffrey P *et al.*: Characterization of SB-269970-A, a selective 5-HT_7 receptor antagonist. *Br. J. Pharmacol.* 130(3), 539–548 (2000).

117 Lovell PJ, Bromidge SM, Dabbs S *et al.*: A novel, potent, and selective 5-HT_7 antagonist: (R)-3-(2-(2-(4-methylpiperidin-1-yl)ethyl)pyrrolidine-1-sulfonyl) phenol (SB-269970). *J. Med. Chem.* 43(3), 342–345 (2000).

118 Thomas DR, Atkinson PJ, Ho M *et al.*: [(3)H]-SB-269970 – a selective antagonist radioligand for 5-HT_7 receptors. *Br. J. Pharmacol.* 130(2), 409–417 (2000).

119 Mnie-Filali O, Faure C, Lambas-Senas L *et al.*: Pharmacological blockade of 5-HT_7 receptors as a putative fast acting antidepressant strategy. *Neuropsychopharmacology* (2011) (Epub ahead of print).

120 Guscott M, Bristow LJ, Hadingham K *et al.*: Genetic knockout and pharmacological blockade studies of the 5-HT_7 receptor suggest therapeutic potential in depression. *Neuropharmacology* 48(4), 492–502 (2005).

121 Hedlund PB, Huitron-Resendiz S, Henriksen SJ, Sutcliffe JG: 5-HT_7 receptor inhibition and inactivation induce antidepressant-like behavior and sleep pattern. *Biol. Psychiatry* 58(10), 831–837 (2005).

■ **First full demonstration of an antidepressant potential for 5-HT_7 receptor antagonists, and more specifically for SB-269970.**

122 Wesolowska A, Nikiforuk A, Stachowicz K, Tatarczynska E: Effect of the selective 5-HT_7 receptor antagonist SB 269970 in animal models of anxiety and depression. *Neuropharmacology* 51(3), 578–586 (2006).

123 Wesolowska A, Kowalska M: Influence of serotonin 5-HT_7 receptor blockade on the behavioral and neurochemical effects of imipramine in rats. *Pharmacol. Rep.* 60(4), 464–474 (2008).

124 Thomas DR, Melotto S, Massagrande M *et al.*: SB-656104-A, a novel selective 5-HT_7 receptor antagonist, modulates REM sleep in rats. *Br. J. Pharmacol.* 139(4), 705–714 (2003).

125 Bonaventure P, Kelly L, Aluisio L *et al.*: Selective blockade of 5-hydroxytryptamine (5-HT)$_7$ receptors enhances 5-HT transmission, antidepressant-like behavior, and rapid eye movement sleep suppression induced by citalopram in rodents. *J. Pharmacol. Exp. Ther.* 321(2), 690–698 (2007).

126 Wesolowska A, Tatarczynska E, Nikiforuk A, Chojnacka-Wójcik E: Enhancement of the anti-immobility action of antidepressants by a selective 5-HT_7 receptor antagonist in the forced swimming test in mice. *Eur. J. Pharmacol.* 555(1), 43–47 (2007).

127 Drew MR, Hen R: Adult hippocampal neurogenesis as target for the treatment of depression. *CNS Neurol. Disord. Drug Targets* 6(3), 205–218 (2007).

128 Faure C, Mnie-Filali O, Haddjeri N: Long-term adaptive changes induced by serotonergic antidepressant drugs. *Expert Rev. Neurother.* 6(2), 235–245 (2006).

129 Paizanis E, Hamon M, Lanfumey L: Hippocampal neurogenesis, depressive disorders, and antidepressant therapy. *Neural Plast.* 2007, 73754 (2007).

130 Chen H, Pandey GN, Dwivedi Y: Hippocampal cell proliferation regulation by repeated stress and antidepressants. *Neuroreport* 17(9), 863–867 (2006).

131 Blier P: Pharmacology of rapid-onset antidepressant treatment strategies. *J. Clin. Psychiatry* 62(Suppl. 15), 12–17 (2001).

132 Czachura JF, Rasmussen K: Effects of acute and chronic administration of fluoxetine on the activity of serotonergic neurons in the dorsal raphe nucleus of the rat. *Naunyn Schmiedebergs Arch. Pharmacol.* 362(3), 266–275 (2000).

133 El Mansari M, Sánchez C, Chouvet G, Renaud B, Haddjeri N: Effects of acute and long-term administration of escitalopram and citalopram on serotonin neurotransmission: an *in vivo* electrophysiological study in rat brain. *Neuropsychopharmacology* 30(7), 1269–1277 (2005).

134 Brenchat A, Romero L, García M *et al.*: 5-HT_7 receptor activation inhibits mechanical hypersensitivity secondary to capsaicin sensitization in mice. *Pain* 141(3), 239–247 (2009).

135 Harsing LG, Prauda I, Barkoczy J, Matyus P, Juranyi Z: A 5-HT_7 heteroreceptor-mediated inhibition of [^{3}H]serotonin release in raphe nuclei slices of the rat: evidence for a serotonergic-glutamatergic interaction. *Neurochem. Res.* 29(8), 1487–1497 (2004).

136 Harsing LG: The pharmacology of the neurochemical transmission in the midbrain raphe nuclei of the rat. *Curr. Neuropharmacol.* 4(4), 313–339 (2006).

137 Hirst WD, Cheung NY, Rattray M, Price GW, Wilkin GP: Cultured astrocytes express messenger RNA for multiple serotonin receptor subtypes, without functional coupling of 5-HT_1 receptor subtypes to adenylyl cyclase. *Brain Res. Mol. Brain Res.* 61(1–2), 90–99 (1998).

138 Shimizu M, Nishida A, Zensho H, Yamawaki S: Chronic antidepressant exposure enhances 5-hydroxytryptamine$_7$ receptor-mediated cyclic adenosine monophosphate accumulation in rat frontocortical astrocytes. *J. Pharmacol. Exp. Ther.* 279(3), 1551–1558 (1996).

139 Schipke CG, Heuser I, Peters O: Antidepressants act on glial cells: SSRIs and serotonin elicit astrocyte calcium signaling in the mouse prefrontal cortex. *J. Psychiatr. Res.* 45(2), 242–248 (2010).

140 Li N, Lee B, Liu R *et al.*: mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* 329(5994), 959–964 (2010).

■ **Evidence that changes in brain plasticity can occur within hours after a single injection of a pharmacological blocker of NMDA receptors.**