Psychopharmacological properties and therapeutic profile of the antidepressant venlafaxine

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Abstract

Major depression (MD) is one of the most common psychiatric disorders worldwide. Currently, the first-line treatment for MD targets the serotonin system but these drugs, notably the selective serotonin reuptake inhibitors, usually need 4 to 6 weeks before the benefit is felt and a significant proportion of patients shows an unsatisfactory response. Numerous treatments have been developed to circumvent these issues as venlafaxine, a mixed serotonin-norepinephrine reuptake inhibitor that binds and blocks both the SERT and NET transporters. Despite this pharmacological profile, it is difficult to have a valuable insight into its ability to produce more robust efficacy than single-acting agents. In this review, we provide an in-depth characterization of the pharmacological properties of venlafaxine from in vitro data to preclinical and clinical efficacy in depressed patients and animal models of depression to propose an indirect comparison with the most common antidepressants. Preclinical studies show that the antidepressant effect of venlafaxine is often associated with an enhancement of serotonergic neurotransmission at low doses. High doses of venlafaxine, which elicit a concomitant increase in 5-HT and NE tone, is associated with changes in different forms of plasticity in discrete brain areas. In particular, the hippocampus appears to play a crucial role in venlafaxine-mediated antidepressant effects notably by regulating processes such as adult hippocampal neurogenesis or the excitatory/inhibitory balance. Overall, depending on the dose used, venlafaxine shows a high efficacy on depressive-like symptoms in relevant animal models but to the same extent as common antidepressants. However, these data are counterbalanced by a lower tolerance. In conclusion, venlafaxine appears to be one of the most effective treatments for treatment of major depression. Still, direct comparative studies are warranted to provide definitive conclusions about its superiority.

Keywords Venlafaxine · 5-HT · NE · Major depression disorder · Antidepressants

Abbreviations

5-HT	5-hydrotryptamine or serotonin
5-HT1A	Serotonin 1A receptor
5-HT1B	Serotonin 1B receptor
$[5\text{-HT}]_{ext}$	Extracellular serotonin
BDNF	Brain-derived neurotrophic factor
CA3	Ammon's horn 3
cFST	Chronic forced swim test
CI	Confidence interval
CNS	Central nervous system
CORT	Corticosterone
CSD	Chronic social defeat
DA	Dopamine
DAT	Dopamine transporter
$[DA]_{ext}$	Extracellular dopamine
DRN	Dorsal raphe nucleus
ED50	Median effective dose
EPM	Elevated plus maze
EZM	Elevated zero maze
FST	Forced swim test
HDRS	Hamilton depressive rating scale
HPA	Hypothalamic–pituitary–adrenal axis
LC	Locus coeruleus
LPS	Lipopolysaccharide
MADRS	Montgomery-Asberg depression rating scale
MD	Mean difference
MDD	Major depressive disorder

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MED   Minimal effective dose
MMP   Matrix metalloproteinase
MS   Maternal separation
NE   Norepinephrine or noradrenaline
NET   Norepinephrine transporter
[NE]$_{ext}$ Extracellular norepinephrine
NNT   Number needed to treat
NRI   Norepinephrine reuptake inhibitor
NSF   Novelty-suppressed feeding
OB   Olfactory bulbectomy
OCT2   Organic cation transporter 2
OF   Open field
OR   Odds ratio
OVX   Ovariectomy
PNN   Perineuronal net
POCD   Post-operative cognitive dysfunction
PV   Parvalbumine
RCT   Randomized clinical trial
RR   Risk ratio
RT50   Recovery time 50
SERT   Serotonin transporter
SMD   Standard mean difference
SNRI   Serotonin-noradrenaline reuptake inhibitor
SPT   Sucrose preference test
SSRI   Selective serotonin reuptake inhibitor
ST   Splash test
TCA   Tricyclic antidepressant
TST   Tail suspension test
UCMS   Unpredictable chronic mild stress
VTA   Ventral tegmental area
WHO   World Health Organization

Introduction

Major depressive disorder (MDD) is a mental disorder characterized by numerous and persistent symptoms such as anhedonia, anxiety, despair, social withdrawal, cognitive deficits, sleep disturbance, and feelings of guilt. According to the World Health Organization (WHO), more than 250 million patients worldwide will suffer from MDD in the coming years. The pathophysiological mechanisms underlying MDD are not yet fully understood, but the monoamine-deficiency hypothesis is now well accepted. This hypothesis stipulates that the occurrence of MDD is associated with deficiencies of the three main monoamine neurotransmitters, namely 5-hydroxytryptamine (5-HT), norepinephrine (NE), and dopamine (DA). On the contrary, stimulating monoaminergic transmission using monoamine reuptake inhibitors or monoamine oxidase inhibitors have proven to be effective in improving mood (Blier 2014). By inhibiting the serotonin transporter (SERT), the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, paroxetine,

or (es)-citalopram block 5-HT reabsorption into neurons, thereby increasing extracellular serotonin concentrations in the synaptic cleft. Although the monoamine-deficiency hypothesis does not fully capture the complex dimension of MDD, efforts are still underway to improve the effectiveness of SSRIs (Liu et al. 2017). It is well documented that this class of antidepressants effectively relieves the symptoms of depression in 60%–65% of the cases. However, a significant proportion of depressed patients does not respond appropriately to these treatments (Rush et al. 2006). Moreover, the remission rate of ~30% is low, and even if antidepressants rapidly increase the extracellular levels of monoamines in the central nervous system (CNS), the first therapeutic signs often take several weeks (i.e., 4–6) to appear.

Owing to the etiological heterogeneity of MDD and the obvious therapeutic limits of SSRIs, it is difficult to conceive that modulating serotonergic neurotransmission alone can generate beneficial and enduring effects in all patients (Hasler 2010). In this context, research in neuropsychopharmacology aims to improve the therapeutic activity of pharmacological drugs that enhance serotonergic tone. It has been postulated that the concomitant inactivation of the SERT and NE transporters (NET) could produce more potent effects than single-acting compounds (Guiard et al. 2009). However, it is still unclear whether adding the noradrenergic component yields more robust antidepressant effects.

This review provides a synthetic overview of current knowledge of the pharmacological properties of venlafaxine from preclinical and clinical studies. Preclinical studies have focused on the mechanisms of action of venlafaxine and its behavioral effects. In contrast, clinical trials or meta-analyses were designed to compare this drug's efficacy with other conventional antidepressant treatment options and highlight its potential superiority.

Pharmacological profile of venlafaxine

The venlafaxine binding profile was initially conducted in vitro and its affinity for different pharmacological targets was evaluated. In rats and humans, a preferential interaction of venlafaxine with SERT compared to NET was reported, whereas its affinity for DAT is very low and insignificant in both species (Bymaster et al. 2001; Millan et al. 2001). Venlafaxine displays a preferential (30-fold higher) affinity for the SERT compared to NET (i.e., KiSERT: 82 nM vs. KiNET: 2480 nM) in the rat brain (Bymaster et al. 2001). The affinity of venlafaxine towards other pharmacological targets involved in the modulation of cerebral monoaminergic neurotransmission (serotonergic, adrenergic, dopaminergic, muscarinic, and histaminergic receptors) was also evaluated. It appears that venlafaxine displays a negligible off-target affinity supporting the idea that it could lack

of side effects, notably those observed with the tricyclics (TCAs).

Regarding its functional activity, venlafaxine blocks the SERT at the dose of 8 mg/kg in mice, while a twice higher dose is necessary to inhibit the NET (Bacq et al. 2012). In line with the latter observations, it inhibits 5-HT reuptake in a potent and robust manner at the dose of 75 mg in depressed patients, whereas higher doses (i.e., 150–225 mg) are required to induce NE reuptake inhibition (Debonnel et al. 2007). These data demonstrate that depending on the dose, venlafaxine can specifically target serotonergic neurotransmission alone or both serotonergic and noradrenergic tones without acting on off-targets.

In vivo preclinical studies of venlafaxine properties

Electrophysiological properties of venlafaxine

The electrophysiological properties of venlafaxine on monoaminergic neurons have been extensively investigated. Due to its ability to block the SERT and the NET, this compound produces a strong impact on both 5-HT and NE systems, associated with different acute and chronic effects. To understand the in vivo electrophysiological properties of venlafaxine, it is essential to bear in mind that monoamine transporters are expressed in presynaptic cell bodies regions (either on collaterals or directly on soma) and nerve terminals. Importantly, the acute inhibition of monoamines transporters reduces neuronal firing rate due to the accumulation of endogenous monoamines around presynaptic inhibitory somatodendritic autoreceptors (Fig. 1, Table 1).

Acute in vivo studies on monoaminergic neurons

Initial electrophysiological studies demonstrate that the acute administration of venlafaxine dose-dependently inhibits the spontaneous firing rate of dorsal raphe nucleus (DRN) 5-HT neurons with an ED50 value of 233 μg/kg i.v. in anesthetized rats (Béïque et al. 1999). Evidence shows that the 5-HT1A receptor antagonist WAY 100635 abolishes this inhibitory response (Millan et al. 2001; Artaiz et al. 2005; Béïque et al. 2000a; Gartside et al. 1997). This demonstrates that venlafaxine leads to an accumulation of 5-HT around 5-HT cell bodies, which in turn, stimulates inhibitory somatodendritic 5-HT1A autoreceptors. Regarding noradrenergic neurons, studies show that they are also dose-dependently inhibited by venlafaxine, but to a lesser degree. Indeed, the spontaneous firing of locus coeruleus (LC) NE neurons is inhibited by venlafaxine with an ED50 of 727 μg/kg i.v (Béïque et al. 1999). This response is abolished in the presence of alpha2-adrenergic receptor antagonist, idazoxan (Berrocoso and

Mico 2007), raising the possibility that the over-activation of inhibitory somatodendritic alpha2-adrenergic receptors mediates such response.

Sub-chronic and chronic in vivo studies on monoaminergic neurons

Single-unit recordings in the rat DRN show that two days of subcutaneous administration of venlafaxine (10 mg/kg) decreases the activity of 5-HT neurons and to a lesser extent, NE neurons (Béïque et al. 2000b), as observed after acute administration (Béïque et al. 1999). In marked contrast, this effect is no longer observed after 21 days of treatment, suggesting a progressive attenuation of the inhibitory feedback exerted by somatodendritic 5-HT1A autoreceptors. This is evidenced by the fact that venlafaxine desensitizes these autoreceptors after 21 days of treatment at doses of 10 to 40 mg/kg (Béïque et al. 2000b). In contrast, single-unit recordings in the LC show that the inhibitory action of venlafaxine persists after 14 and 21 days of treatment (10–40 mg/kg). Although the reasons for such differences between the 5-HT and NE systems remain debatable, it was proposed that the somatodendrtic alpha-2-adrenergic autoreceptors do not have the peculiarity to desensitize (Berrocoso and Mico 2007; Béïque et al. 2000c).

The latter consideration is important since the time required for serotonergic antidepressants to desensitize somatodendritic 5-HT1A autoreceptors and thereby to significantly increase 5-HT neuronal firing, coincides with their onset of therapeutic activity. Consequently, given that venlafaxine displays the same electrophysiological properties than SSRIs in term of firing recovery, it is not surprising that the delay in venlafaxine response is similar to that of SSRIs. The lack of alpha2 adrenoceptor desensitization may be counterproductive for the beneficial effect of venlafaxine in term of efficacy or delay of action. In agreement with this hypothesis, electrophysiological studies showed that the pharmacological inactivation of alpah2 adrenoceptor with mirtazapine produces a rapid increase in noradrenergic but also serotonergic neurotransmission (Haddjeri et al. 1995). The latter results led to the hypothesis that the combination of venlafaxine with mirtazapine could produce more rapid improvement of depressive symptoms compared to SSRI alone. The interest for such combination derives from studies of mirtazapine augmentation of a variety of antidepressant agents (principally SSRIs) rather than specifically of venlafaxine (Carpenter et al. 1999, 2002).

In vivo studies on postsynaptic monoaminergic neurons

At the nerve terminals and particularly in the hippocampus, postsynaptic pyramidal CA3 neurons are sensitive to 5-HT and NE. These post-synaptic neurons express 5-HT1A and
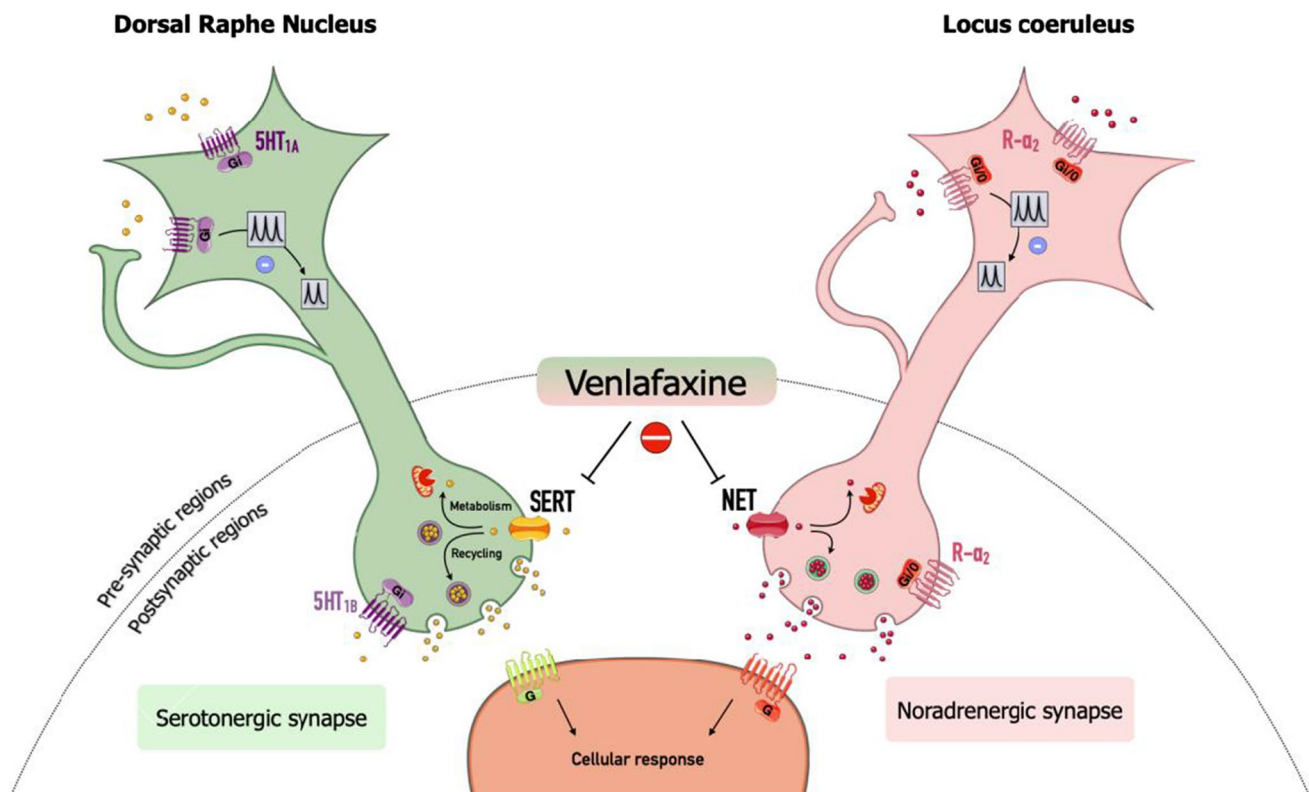
Fig. 1 Mechanism of action of Venlafaxine. 5-HT and NE are stored into presynaptic vesicles. Incoming action potentials trigger their release into the synaptic cleft after melding with the cell membrane. 5-HT/NE can then bind to postsynaptic serotonergic and adrenergic G-coupled receptors. In parallel of the activation of these postsynaptic elements, 5-HT/NE can return into the presynaptic neurons through serotonin/norepinephrine transporters (SERT/NET) through a high affinity reuptake process. 5-HT/NE can also be removed from the synaptic cleft by neighboring glial cells such as astrocytes (not shown here). Into the presynaptic neuron, 5-HT and NE can penetrate into exocytosis vesicles through a vesicular monoamine transporter or degraded by the monoamine oxidase (MAO). Serotonergic and noradrenergic neurons have multiple ways to up- and downregulate monoamines response thereby maintaining a normal excitatory/inhibitory balance and protecting the brain from a sub-or over-stimulation.

Receptors are not only found on the postsynaptic neuronal membrane, but also presynaptically. In particular, autoreceptors are found on axon terminals (i.e. 5HT1B and A2R) or on the soma (i.e. 5HT1A and A2R). If too many neurotransmitters accumulate in the synaptic cleft, these Gi-coupled autoreceptors are activated to mediate an inhibitory signal on the firing or release activities of the presynaptic serotonergic and adrenergic neurons. By inhibiting the SERT and NET transporters, venlafaxine can simultaneously increase extracellular 5-HT/NE levels in various brain regions involved and therefore to activate postsynaptic receptors involved in the regulation of emotional states. However, this action is limited by the recruitment of the autoreceptors after an acute administration of venlafaxine. While the treatment is prolonged, such inhibitory feedbacks desensitize thereby producing a higher rate of monoamines in the synaptic cleft necessary to promote beneficial behavioral effects.

alpha-2 heteroreceptors which mediate inhibitory responses. Accordingly, acute intravenous administration of venlafaxine (5 mg/kg) in rats results in a massive (73%) suppression of CA3 pyramidal neurons firing, similar to the effects of the SSRI paroxetine (Béïque et al. 2000b). Interestingly, this effect is reversed by the 5-HT1A antagonist WAY100635 (Béïque et al. 2000b). Hence, any increase in extracellular 5-HT levels, but also of NE, results in the progressive attenuation of postsynaptic neuronal activity. This property has been successfully used to assess the in vivo potency of pharmacological agents known to inhibit monoaminergic transporters. Indeed, the time required for the firing activity to recover 50% of the initial firing rate after application of 5-HT or NE (recovery time: RT50 value) is an indication

of reuptake inhibitors' ability to maintain 5-HT and/or NE in the synaptic cleft. The higher the RT50 value, the higher the ability to block the transporters. Of note, the subcutaneous administration of venlafaxine at 16 mg/kg significantly increased the RT50 after the microiontophoretic application of 5-HT or NE (Bacq et al. 2012). This highlights the ability of venlafaxine to prolong inhibitory actions of 5-HT and NE onto CA3 pyramidal cells by blocking their respective transporters. Interestingly, the genetic depletion of the organic cation transporter 2 (OCT2), a transporter exhibiting low affinity for monoamines, potentiates venlafaxine-induced increase in RT50 (Bacq et al. 2012). This suggests that residual 5-HT and NE could be removed from the synaptic cleft by OCT2.

Table 1 Synthesis of the electrophysiological properties of venlafaxine on monoaminergic neurons. Venlafaxine was delivered either by systemic (i.v.) or delivered by osmotic pump. Electrophysiological recordings were performed within the dorsal raphe nucleus, locus coeruleus, and ventral tegmental area which are the place of mono- aminergic neuron cell bodies (respectively 5-HT, NE, and DA). *Extrapolation of ED50 value from dose-effect curve. Arrows (↓) mean that venlafaxine induces a decrease in neuronal firing rate, while (=) means that the discharge rate remains unchanged

Model	Duration of treatment	Route of administration	Recording site	Methods	Electrophysiological effect	References
Wistar rats	Acute	i.v.	VTA	Dose effect curve	=N.A.	(Millan et al. 2001)
Sprague Dawley rats	Acute	i.v.	DRN	Dose effect curve	↓ ED50= 233 ± 12 µg/kg	(Béïque et al. 1999)
Wistar rats	Acute	i.v.	DRN	Dose effect curve	↓ ED50= 125 µg/kg *	(Millan et al. 2001)
Wistar rats	Acute	i.v.	DRN	Dose effect curve	↓ ED50= 358 ± 44 µg/kg	(Artaiz et al. 2005)
Sprague Dawley rats	Acute	i.v.	DRN	Dose effect curve	↓ ED50= 160 ± 23 µg/kg	(Gartside et al. 1997)
Sprague Dawley rats	Acute	i.v.	LC	Dose effect curve	↓ ED50= 1800 µg/kg	(Berrocoso and Mico 2007)
Sprague Dawley rats	Acute	i.v.	LC	Dose effect curve	↓ ED50= 737 ± 68 µg/kg	(Béïque et al. 1999)
Wistar rats	Acute	i.v.	LC	Dose effect curve	↓ ED50= 1000 µg/kg *	(Millan et al. 2001)
Sprague Dawley rats	2-day	osmotic pump (10 mg/kg)	DRN	Basal firing rate recording	↓ N.A.	(Béïque et al. 2000b)
Sprague Dawley rats	2-day	osmotic pump (10-40 mg/kg)	LC	Basal firing rate recording	↓ N.A.	
Sprague Dawley rats	14-day	osmotic pump (40 mg/kg)	LC	Dose effect curve	↓ ED50= 2000 ± 500 µg/kg	(Berrocoso and Mico 2007)
Sprague Dawley rats	21-day	osmotic pump (10 mg/kg)	DRN	Basal firing rate recording	=N.A.	(Béïque et al. 2000b)
Sprague Dawley rats	21-day	osmotic pump (10-40 mg/kg)	LC	Basal firing rate recording	↓ N.A.	

Chronic administration of venlafaxine (21 days by osmotic minipumps at either 10 or 40 mg/kg/day) increases RT50 for 5-HT (Béïque et al. 2000b). The authors show an enhancement of serotonergic neurotransmission after 21-days of treatment with venlafaxine, and this effect is only achieved under conditions where the desensitization of the terminal 5-HT1B autoreceptors is appended to the somatodendritic 5-HT1A receptors (Béïque et al. 2000b). Remarkably, RT50 for NE is increased only at the dose of 40 mg/kg/day, corroborating a preferential effect on SERT inhibition over NET inhibition (Béïque et al. 2000b). Taken together, these data confirm the above-mentioned in vitro data that venlafaxine blocks the reuptake of 5-HT and to a lesser degree NE.

Taken together, these data suggest that venlafaxine blocks 5-HT and NE reuptake processes but its potency to target the 5-HT system is greater compared to the NE system. At low doses, venlafaxine act as an SSRI whereas higher doses are required to impact both systems. Chronic administration of venlafaxine leads to an overall increased 5-HT neurotransmission in response to a progressive desensitization of somatodendritic 5-HT1A autoreceptors as classical antidepressant drugs do (Quentin et al. 2018). Interestingly, although a 21-day treatment of venlafaxine desensitizes somatodendritic and terminal 5-HT1A/1B autoreceptors, it fails to do so on alpha2-adrenergic autoreceptors. This agrees with previous studies showing that different classes of antidepressants such as the NRI reboxetine but also the IMAO and the TCA do not modify the functional sensitivity of alpha2-adrenoceptors even after sustained administration (Blier and de Montigny 1985; Lacroix et al. 1991; Szabo and Blier 2001).

Neurochemical properties of venlafaxine

The neurochemical effects of venlafaxine on extracellular monoamines have been assessed in different brain structures using in vivo microdialysis in rodents.

In the rat frontal cortex, Millan and collaborators examined the acute effects of increasing doses of subcutaneous venlafaxine on the extracellular concentrations of the three monoamines ([5-HT]ext, [NE]ext, and [DA]ext).

In agreement with venlafaxine ability to block the SERT and the NET, the authors observed a significant and dose-dependent increase of [5HT]ext starting from 0.63 mg/kg up to 40 mg/kg of venlafaxine with a maximal increase of 400% from baseline. Likewise, venlafaxine increases [NE]ext approximately by 500% which remains elevated for up to 3 hours after subcutaneous administration of the antidepressant at the dose of 40 mg/kg. Although venlafaxine has no affinity for the DAT, increases of cortical [DA]ext are also detected in response to venlafaxine from 2.5 mg/kg up to 40 mg/kg (Millan et al. 2001). It was proposed that the pharmacological inactivation of the NET might prevent DA reuptake by a heterologous reuptake process (Guiard et al. 2008; Morón et al. 2002). Regarding NE, a significant increase of [NE]ext was detected in the rat brain following administration of 3 to 30 mg/kg of venlafaxine (Koch et al. 2003; Beyer et al. 2002). Similar results were obtained from mice in which intraperitoneal administration of venlafaxine at the dose of 30 mg/kg also increased the cortical extracellular concentrations of the three monoamines (Higashino et al. 2014). In mice, the effects of venlafaxine on [5HT]ext (but not on [NE]ext) were even observed at a lower dose (i.e. 8 mg/kg) (David et al. 2003). It should be noted that all these data originate from non-depressed mice. In the rat hippocampus, another brain region critically involved in MDD, the acute subcutaneous administration of venlafaxine (5, 10, and 20 mg/kg) fosters [5HT]ext and [NE]ext (Millan et al. 2001; Sánchez et al. 2007). In the rat striatum and nucleus accumbens, venlafaxine (10 mg/kg, s.c) induces an increase in [5HT]ext whereas [DA]ext remains unchanged (Millan et al. 2001).

Only a few studies assessed the effect of chronic venlafaxine on monoaminergic neurotransmission. Surprisingly, a 14 or 21 day-period of subcutaneous or intraperitoneal administration of venlafaxine at the doses of 10 and 30 mg/kg does not affect cortical [5HT]ext, [NE]ext, and [DA]ext basal levels (Millan et al. 2001; Higashino et al. 2014). Gur and colleagues also evaluated the effect of the intraperitoneal administration of venlafaxine at the dose of 5 mg/kg for 28 days and again, they did not observe significant effects on [5HT]ext (Gur et al. 1999). However, another study reports that the chronic subcutaneous administration of venlafaxine for 14 days at the dose of 10 mg/kg increases cortical [5HT]ext and [NE]ext and that such effects could be potentiated by an OCT2 pharmacological blocker (Rahman et al. 2008). This finding further confirms that OCT2 contributes to the clearance of the remaining 5-HT and NE in the synaptic cleft.

To conclude, it appears that acute venlafaxine has a positive impact on monoaminergic systems due to its ability to block the SERT and the NET. These transporters are present in brain regions involved in the regulation of mood and their pharmacological blockade enhances extracellular 5HT and NE levels. Evidence also suggests that venlafaxine may act on dopaminergic transmission through the inactivation of a heterologous reuptake process involving the NET, notably in the frontal cortex. An increase in monoamine levels is also observed in the cell body areas (i.e., in the DRN and LC) and this favors the importunate binding and activation of inhibitory 5HT1A/alpha2 autoreceptors. Surprisingly and contrary to what is observed in electrophysiological studies, microdialysis data do not show a preferential effect of venlafaxine on [5HT]ext compared to [NE]ext (even at low doses) excepted in one study (David et al. 2003). In these microdialysis experiments, literature reports a great variability from one study to another that could depend on different parameters. Although neurochemical data come from rat studies, we noticed differences between species in response to venlafaxine treatment. One might ask whether the levels of expression of the SERT and/or NET is different in rats and mice for example. Doses and routes of administration could be other factors determining the impact venlafaxine on the 5-HT and NE systems. Finally, the precise site of implantation of the microdialysis probes could also be a critical point because brain structures display different monoaminergic inputs and different levels of monoaminergic transporters.

Regarding chronic exposure, electrophysiological studies report a functional desensitization of 5-HT1A autoreceptors after chronic venlafaxine treatment. However, this effect is not accompanied by an enhancement of serotonergic neurotransmission. A large number of studies have failed to show increases in basal 5-HT level in terminal areas after chronic administration of venlafaxine but also with other 5-HT reuptake inhibitors, unless the sample collections were performed less than 24 h after the last drug administration (Bel and Artigas 1993; Kihara and Ikeda 1995; Bosker et al. 1995; Invernizzi et al. 1995, 1996; Hjorth and Auerbach 1999; Jaskiw et al. 2006). This lack of effect could reflect adaptive changes. Indeed, according to the homeostasis rules, it is possible the release process is attenuated. 5-HT synthesis and degradation can also be modified which could explain this lack of significant action of venlafaxine on 5-HT tone. Finally, it is important to note that there are no studies assessing the chronic effects of venlafaxine on animal models of depression. One would expect that chronic venlafaxine could exert its beneficial effects specifically in pathological conditions characterized by low extracellular 5-HT levels. Another explanation can be a technical issue with intracerebral microdialysis. It is well known that the gold standard technique to probe monoaminergic tone after chronic exposure is the "no net flux" (Guiard et al. 2005) but this approach was not applied in the currently available publications.

Behavioral effects of venlafaxine

Preclinical studies have explored its antidepressant properties in naïve non-stressed animals and in various animal models of depression. These include animals submitted to unpredictable chronic mild stress (UCMS), chronic social defeat (CSD), maternal separation (MS), olfactory bulbectomy (OB), ovariectomy (OVX), or prolonged administration of corticosterone (CORT). This part of the review focuses on the behavioral effects of venlafaxine on mice.

In naïve mice

The efficacy of venlafaxine on mice depressive-like behavior was mainly evaluated using the FST and the TST tests and a wide range of doses was screened (from 1 up to 80 mg/kg). Michel Bourin's group was the first to evaluate the behavioral effects of venlafaxine in mice and reported that its acute venlafaxine (8 to 64 mg/kg) elicits antidepressant-like effects in the FST and TST as evidenced by a reduction of animal's immobility time. This study also showed that 8 mg/kg of venlafaxine blocks 5-HT reuptake inhibition, while doses above 16 mg/kg seem to inhibit the SERT and the NET (Redrobe et al. 1998). Such beneficial effects are unlikely to result from a psychostimulant effect since high doses of venlafaxine do not influence locomotor activity (Berrocoso and Mico 2007). Of note, most of the subsequent studies did not demonstrate the antidepressant-like effects of venlafaxine when doses below 8 mg/kg were used (Bortolatto et al. 2010; Castagné et al. 2009; Bourin et al. 2009; David et al. 2001) (Table 2). However, some studies report beneficial effects of venlafaxine intraperitoneal administration at doses of 4 (Kulkarni and Dhir 2007) (Table 2). To explain these mixed results, the importance of mice strain and gender was explored (variables not shown in Table 2). It appears that most studies used males and that C57BL6 and albino (CD1/SWISS/LACA) mice were more prone to respond to low doses (<8 mg/kg) of venlafaxine. The mode of administration could be another important parameter of venlafaxine efficacy since in acute experiments performed in mice, its antidepressant-like effects appear at 80 mg/kg but not at 20 mg/kg when oral administration was performed (Yamada et al. 2013).

Collectively, these data suggest that in non-pathological conditions, the acute administration of venlafaxine produces antidepressant-like effects at doses ranging from 8 to 80 mg/kg and that the expression of its beneficial effects does not necessarily require the noradrenergic system.

With respect to sub-chronic (< 7 days) administration, two studies tested whether prolonged treatment with venlafaxine could produce more robust effects than those observed after acute administration (Ren et al. 2018; Ide et al. 2010). It is noteworthy that the antidepressant-like effects of venlafaxine (10 mg/kg; i.p.) were observed in both FST and TST, following daily drug administration for three consecutive days (Ren et al. 2018). In another work, venlafaxine was administered for 5 days at either 10 or 30 mg/kg, and despair was evaluated each day in the FST (Ide et al. 2010). Remarkably, at 10 mg/kg, venlafaxine produced antidepressant-like effects observable from the first day of treatment, and this response persisted to the fourth day. In contrast, at 30 mg/kg, venlafaxine triggered antidepressant-like effects only after 3 and 4 days of treatment. Considering these data, one would anticipate that chronic administration of venlafaxine also promotes positive effects in the FST and TST. Indeed, such beneficial effects were observed from the seventh day of treatment in the TST and after 2 weeks of exposure in the FST and TST (Liu et al. 2012). It is plausible that such delay coincides with the time required for the cellular and structural adaptations that underlie the therapeutic effect of antidepressants and contribute to the adaptive plasticity induced in the brain by these drugs. In another study, 2 weeks of venlafaxine at the dose of 16 mg/kg had no antidepressant-like effect (Liang et al. 2016). However, after 3 weeks of treatment, venlafaxine 4 (Thomas et al. 2016a) and 5 (Abdel-Wahab and Salama 2011) mg/kg elicited antidepressant-like effects in the FST and TST. Higher doses were also tested (10–20 mg/kg), revealing a dose-response relationship (Abdel-Wahab and Salama 2011). After 4 weeks of treatment with venlafaxine (10 mg/kg, p.o.) antidepressant-like effects were also observed in the TST (Carlini et al. 2012). Although interesting, these data focused on despair and further experiments are needed to determine whether venlafaxine also acts on other symptoms of depression.

The acute anxiolytic effect of venlafaxine was assessed using a large spectrum of concentrations (i.e. 10 – 60 mg/kg) and found from 30mg/kg (Li et al. 2006). Despite the beneficial effect on anxiety of a single administration of venlafaxine, several studies failed to demonstrate anxiolytic-like effects of this drug when administered chronically. Indeed, 2 or 4 weeks of venlafaxine at the dose of 10 or 16 mg/kg had no effect on the time spent in the open arms or in the center of the arena in the EPM, OF, or EZM test whereas some studies reported beneficial effects after the administration of the SSRIs fluoxetine and paroxetine or the SNRI duloxetine (Carlini et al. 2012; Hu et al. 2018; Mirza et al. 2007).

Altogether, studies using acute, sub-chronic, and chronic administration of venlafaxine in naive mice suggest that over 8 mg/kg, venlafaxine elicits antidepressant-like effects on despair (Table 2). Furthermore, additional anxiolytic effects of venlafaxine are observed after acute administration when administered at high dose, whereas prolonged treatment does not. Moreover, when many doses were evaluated, several studies observed a dose-response relationship with greater effects in response to high doses and this could be correlated

Table 2 Antidepressant-like effects of venlafaxine in naïve, non-depressed mice. *FST*, forced swim test; *TST*, tail suspension test; *EPM*, elevated plus maze; *OF*, open field; *EZM*, elevated zero maze; *NSF*, novelty-suppressed feeding test; *SPT*, sucrose preference test.

Strain	Acute vs. chronic	Dose–route of administration	Behavioral test	Behavioral effect	References
Swiss mice	Acute	1–2–4–8–16–32–64 mg/kg	FST	Antidepressant effect from 8 mg/kg	(Redrobe et al. 1998)
Swiss mice	Acute	2 mg/kg; i.p.	FST	Antidepressant effect	(Socała et al. 2012)
Swiss mice	Acute	2–8 mg/kg; i.p	FST	Antidepressant effect only at 8 mg/kg	(Bortolatto et al. 2010)
NMRI mice	Acute	2–4–8–16–32–64 mg/kg; i.p.	FST	Antidepressant effect from 8 mg/kg	(Castagné et al. 2009)
Swiss mice	Acute	4–8–16 mg/kg; i.p.	FST	4-week-old mice: antidepressant effect 8 mg/kg	(David et al. 2001)
				40-week-old mice: antidepressant effect only at 16 mg/kg	
Laca mice	Acute	4–8–16 mg/kg; i.p.	FST	Antidepressant effect	(Kulkarni and Dhir 2007)
Swiss mice	Acute	4–8–16 mg/kg; i.p.	FST	Antidepressant effect only at 16 mg/kg	(Bourin et al. 2009)
Swiss mice	Acute	10–20–40 mg/kg; i.p.	TST - FST	Antidepressant effect at 20 and 40 mg/kg only in FST	(Auclair et al. 2013)
CD1 mice	Acute	10–30–60 mg/kg; p.o.	FST - TST	Antidepressant effect from 30 mg/kg	(Artaiz et al. 2005)
Swiss mice	Acute	10 up to 60 mg/kg; i.p.	Marble - Nestlet shredding	Anxiolytic effect from 30 mg/kg	(Li et al. 2006)
ICR mice	Acute	20–80 mg/kg; per os	FST	Antidepressant effect at 80 mg/kg	(Yamada et al. 2013)
C57BL/6J mice	Acute / 3 days	10 mg/kg; i.p.	TST / FST	Antidepressant effect	(Ren et al. 2018)
C57BL/6J mice	1 to 5 days	10–30 mg/kg; s.c.	FST	10 mg/kg: antidepressant effect day 1 to 4	(Ide et al. 2010)
				30 mg/kg: antidepressant effect day 3 and 4	
Swiss mice	7–14–21 days	4 mg/kg; i.p.	TST - FST	Antidepressant effect	(Thomas et al. 2016b)
ICR mice	7–14 days	9.4 mg/kg; i.p.	FST - TST	Antidepressant effect at 7 days only in TST and 14 days in both tests	(Liu et al. 2012)
C57BL/6J mice	14 days	16 mg/kg; i.p.	EPM – OF - SPT	No anxiolytic but hedonic effect	(Hu et al. 2018)
C57BL/6J mice	14 days	16 mg/kg; i.p.	SPT / TST	Hedonic effect	(Liang et al. 2016)
Swiss mice	21 days	5–10–20 mg/kg; i.p	FST - TST	Antidepressant effect	(Abdel-Wahab and Salama 2011)
Swiss mice	28 days	10 mg/kg; p.o.	TST / OF	Antidepressant effect / No anxiolytic effect	(Carlini et al. 2012)
NMRI mice	28 days	10 mg/kg; p.o	EZM	No effect	(Mirza et al. 2007)

with electrophysiological or neurochemical measures. This dual effect of venlafaxine on serotonergic (low/high doses) and noradrenergic (only high dose) can explain such a dose-response relationship.

In mouse models of depression

A review of the literature reveals a dozen of publications evaluating the effects of venlafaxine in mouse models of

depression. Among them, 3 used the chronic forced swimming test (cFST) model which involves subjecting mice to repeated swimming stress. In one study, mice are submitted to this protocol for 21 consecutive days while receiving low doses of venlafaxine (from 2 to 16 mg/kg; i.p.)(Thomas et al. 2016a). Antidepressant-like effects in the FST and tail suspension test (TST) were observed only after 3 weeks of treatment at the dose of 4 mg/kg. At higher doses (8 and 16 mg/kg), the antidepressant-like effects occur after 2 weeks of treatment (Thomas et al. 2016a, 2017). In another study, the cFST is applied for one week while mice receive venlafaxine at doses of 5 and 10 mg/kg. An immediate beneficial effect persisting for seven days was revealed (Kumar et al. 2010). At the end of this experimental procedure, anxiolytic effects were also found in the elevated plus maze (EPM) and the mirror chamber test (approach-avoidance test when animals are confronted by a mirror), whatever the dose administered (5 and 10 mg/kg; i.p.) (Kumar et al. 2010).

The behavioral effects of venlafaxine were also tested in the chronic social defeat (CSD) model of depression which consists in repeatedly exposing naïve mice to aggressor mice. Venzala and colleagues treated mice with venlafaxine for 4 weeks at a dose of 20 mg/kg (i.p.) before submitting them to a battery of behavioral tests. They observed antidepressant-like effects in the FST and sucrose preference test (SPT), anxiolytic responses in the EPM and novelty-suppressed feeding (NSF). However, venlafaxine did not abolish the deficit in the social interaction test (Venzala et al. 2012). In a different study, mice were treated with venlafaxine for six weeks at the dose of 16 mg/kg (i.p.) before evaluating their behavior (Bai et al. 2017). While no antidepressant nor anxiolytic effects were seen in the FST and TST or EPM, an improved capacity for social interaction was observed in these animals (Bai et al. 2017). Moreover, in postoperative cognitive dysfunction (POCD), venlafaxine (16 mg/kg; i.p.) was shown to increase working memory in the Y-maze (Li and Zhang 2021). Furthermore, mice submitted to mechanical and cold hyperalgesia induced by repeated injection of oxaliplatin, developed traits characteristic of an anxiety-depressive phenotype, whereas the acute venlafaxine treatment (16 mg/kg, s.c) alleviated neuropathic pain and promoted antidepressant-like effects in these animals (Hache et al. 2015). In summary, the 16 mg/kg i.p. chronically administered is the optimal dose to treat depression andanxiety but also to improve cognitive performances in several animal models of depression.

In two other studies, mice submitted to the Unpredictable chronic mild stress (UCMS) were used to address venlafaxine's antidepressant properties. After 7 days of venlafaxine (10 mg/kg, i.p.) treatment, antidepressant-like effects were observed in the FST and TST, while only 3 days of treatment were not sufficient to elicit such effects (Ren et al. 2018). As expected, in UCMS mice, prolonged venlafaxine treatment (i.e., 2 weeks, i.p.) using the same dose also produced antidepressant-like effects, notably by improving social interaction (Wang et al. 2020).

Chronic administration of corticosterone (CORT) in the drinking water of mice is a widely used model of depression, which allows screening the effects of antidepressant drugs. For instance, an 8-week period of CORT exposure induces depressive-like behaviors which are reversed by monoaminergic antidepressant drugs (David et al. 2009). Indeed, 3 weeks (16mg/kg) chronic administration of venlafaxine exerted antidepressant- and anxiolytic-like effects in the splash test (ST) and the zero maze respectively (Bacq et al. 2012). Interestingly, studies showed that ovariectomy (OVX)-induced depressive-like symptoms in females are reversed by long-term intragastric administration of venlafaxine. In a first study, depressive-like behaviors occurred 8 weeks only after ovariectomy, and venlafaxine (70 mg/kg, intragastric) therapeutic action in the TST is observed as early as after 1 and 2 weeks of treatment in OVX mice compared to vehicle mice while depressive-like behavior occurred only 8 weeks after ovariectomy (Ye et al. 2016). More recently, these authors reported that intragastric administration of venlafaxine (9.75 mg/kg) in OVX females had no effect in the EPM (Xu et al. 2019). Lastly, Poretti et al. (2016) used bulbectomy-induced depressive-like behavior in mice. In this model, the oral administration of venlafaxine (5 to 20 mg/kg) elicited antidepressant effects in the TST after 3weeks of chronic treatment at the highest dose (20 mg/kg) while antidepressant effects were observed after 4weeks of treatment at 10 to 20 mg/kg (Poretti et al. 2016). The lowest dose (5 mg/kg) did not induce a change in immobility time in this test.

The literature review indicates that venlafaxine displays antidepressant-like effects in various mouse models of depression, when administered acutely, sub-chronically as well as chronically (Table 3). The effective dose, i.e., the dose that promotes beneficial behavioral effects on anxiety, was found to start at 8 mg/kg, although a few studies have documented antidepressant-like effects at lower doses. This indicates that targeting the 5HT system is sufficient to elicit beneficial effects and there is no evidence showing that a high dose of venlafaxine promotes greater antidepressant-like responses. The possibility that low and high doses promote distinct effects warrant further investigations. Furthermore, the different routes of administration (i.p. vs. p.o.) elicit similar behavioral effects in the mouse models of depression. Finally, treatment duration is another parameter that should be considered. Most studies show that venlafaxine becomes effective after a minimum of 3 weeks of treatment, as is the case with conventional antidepressants (i.e., SSRI).

Table 3 Antidepressant-like effects of venlafaxine in different mouse models of depression. *FST*, forced swim test; *TST*, tail suspension test; *EPM*, elevated plus maze; *OF*, open field; *EZM*, elevated zero maze; *NSF*, novelty-suppressed feeding test; *SPT*, sucrose preference test; *YM*, Y-maze; *OVX*, ovariectomized female mice; *UCMS*, unpredictable chronic mild stress. Route of administration: i.p. for intraperitoneal, p.o. for per os.

Strain	Model of depression	Treatment duration	Dose–Route of administration	Behavioral test	Behavioral effect	References
Laca mice	Chronic FST	1 to 7 days	5–10 mg/kg; i.p.	FST	Antidepressant effect in FST from 1 day	(Kumar et al. 2010)
				EPM – Mirror chamber test	Anxiolytic effect	
Swiss mice	Chronic FST	7–14–21 days	2–4–8–16 mg/kg; i.p.	FST - TST	14 days: Antidepressant effect from 8 mg/kg	(Thomas et al. 2016a)
					21 days: Antidepressant effect at each dose	
Swiss mice	Chronic FST	7–14–21 days	2–4 mg/kg; i.p.	FST	Antidepressant effect after 21 days of venlafaxine 4 mg/kg	(Thomas et al. 2017)
ICR mice	OVX	1–2 -8 weeks	71.92 mg/kg; p.o..	TST	Antidepressant effect after 1 weeks	(Ye et al. 2016)
ICR mice	OVX	8 weeks	9.75 mg/kg; p.o.	EPM	No effect	(Xu et al. 2019)
C57BL/6J mice	UCMS	3–7 days	10 mg/kg; i.p.	TST – FST - SPT	Antidepressant effect only at 7 days	(Ren et al. 2018)
C57BL/6J mice	UCMS	2 weeks	10 mg/ kg; i.p.	FST - TST	Antidepressant effect	(Wang et al. 2020)
C57BL/6J mice	Chronic social defeat	30 days	20 mg/kg; i.p.	FST	Antidepressant effect in FST	(Venzala et al. 2012)
				OR - EPM - NSF- Social - SPT	Anxiolytic and Hedonic effect in EPM and NSF	
C57BL/6J mice	Chronic social defeat	6 weeks	16 mg/kg; i.p.	SPT - OF - TST - EPM - YM - FST	No effect	(Bai et al. 2017)
C57BL/6J mice	CORT	21 days	16 mg/kg; i.p.	SPT - O maze - Coat state - ST	Anxiolytic effect – Hedonic effect – Decrease mice coat degradation/ Reverse mice coat degradation	(Bacq et al. 2012)
Swiss mice	Bulbectomy	14–21–28 days	5–10–20 mg/ kg; p.o.	TST	Antidepressant effect from 21 days (20mg/kg) and at 28 days (10–20mg/kg)	(Poretti et al. 2016)

Effects of venlafaxine on sleep

Links between sleep, depression, and antidepressant treatments are strong. About three-quarters of depressed patients have insomnia symptoms, and hypersomnia is present in about 40% of young depressed adults. As well as the subjective experience of sleep symptoms, there are well-documented changes in sleep architecture in depression (Nutt et al. 2008). Evidence shows that sleep architecture is modified by an increase in rapid eye movement (REM) sleep propensity in the early night resulting in an increased REM sleep quantity and sleep fragmentation. This leads to poor sleep quality (Grønli et al. 2004). Interestingly, venlafaxine is able to modify sleep architecture. For instance, in naïve rats, it was shown that venlafaxine produces a dose-related suppression of REM sleep as TCA or SSRIs do (Wichniak

et al. 2017). Venlafaxine also increases wake time (Salin-Pascual and Moro-Lopez 1997). Although these effects were found in non-depressed rodents, the reduction of total sleep duration and sleep efficiency (hypersomnia) observed in the mouse CORT model of depression (Le Dantec et al. 2014) strongly suggests that venlafaxine could have a beneficial action on this parameter, notably due to its neurochemical properties. Indeed, at the neurochemical levels, it is well known that the serotonergic and noradrenergic systems are involved in the regulation of sleep and wakefulness, their activity being at maximum during the awake state and minimum during sleep (Adrien 2002). Because the production of REM sleep depends on the decrease of serotonergic and noradrenergic tones in brain stem structures, it is possible that the ability of this antidepressant to favor inhibition of REM relies on its ability to increase monoaminergic tone. Evidence demonstrated that both SSRIs and SNRIs have the same effects on the suppression of REM (Wichniak et al. 2017) suggesting that the elevation of 5-HT neurotransmission is sufficient to impact this parameter and therefore to counterbalance sleep disturbances observed in depression. Whether or not the effects of venlafaxine on sleep differ according to the dose and its ability to increase 5-HT and/or NE extracellular levels has yet to be solved.

Mechanism of action venlafaxine: emphasis on brain plasticity

Impact of venlafaxine on adult hippocampal neurogenesis

Ex vivo studies evaluated the influence of animal models of depression on Brain-Derived Neurotrophic Factor (BDNF). They showed that corticosterone, mimicking an increased HPA reactivity and LPS induce a significant reduction of BDNF gene and protein expression in the frontal cortex and hippocampus (Lin et al. 2019; Huang et al. 2011). Going one step further, several studies evaluated the effects of venlafaxine on BDNF expression and on hippocampal adult neurogenesis. After 7 days of administration, venlafaxine increases BDNF expression in the hippocampus (Larsen et al. 2008) while fluoxetine fails to do so. In another study, 7 days of venlafaxine (10 mg/kg, p.o.) fails to modify hippocampal or cortical BDNF protein level (Cooke et al. 2009). Nevertheless, the authors reported enhanced cortical BDNF protein levels in response to the chronic administration of venlafaxine (21 days, 10 mg/kg, p.o.), while citalopram had no effect. Cortical and hippocampal BDNF levels were also increased after a 5-week period of venlafaxine treatment in rat (20 mg/kg, p.o) (Czubak et al. 2009). Interestingly, a 28-day period of venlafaxine treatment (10 mg/kg, p.o.)

followed by 28 days of chronic restrained stress (CRS) without treatment in rat, enhanced BDNF expression (Lapmanee et al. 2017). In the same model of depression, systemic administrations of venlafaxine (5 mg/kg) for 14 and 21 days rescued hippocampal BDNF expression (Xu et al. 2004). Following UCMS, a marked increase of BDNF was observed in the rat hippocampus after 28 of venlafaxine(Wang et al. 2020; Huang et al. 2014).

Regarding the influence of venlafaxine on hippocampal neurogenesis, it was shown that the administration of a high (but not low) dose of venlafaxine (40 mg/kg) for 14 days increased cell proliferation in the dentate gyrus of rats (Mostany et al. 2008). In the Chronic Restraint Stress (CRS) rat model, a 21-day treatment with venlafaxine (5 mg/kg, i.p.) rescues the impairment of hippocampal progenitors' proliferation (Xu et al. 2004). Accordingly, Zhang and colleagues showed that the deleterious effects of UCMS on hippocampal cell proliferation were abolished by 21 days of venlafaxine (15 mg/kg, i.p.) (Zhang et al. 2015). Similar effects were found in the MS and UCMS models of depression after 14 days of venlafaxine treatment (respectively 20 & 5 mg.kg; p.o.) (Belovicova et al. 2017; Martisova et al. 2015).

Another important step of adult neurogenesis is the survival of adult-born cells. While the expression of pro-apoptotic or anti-apoptotic molecules such as Bax or Bcl-xl are respectively up- and downregulated in the hippocampus of UCMS submitted animals, a 21-day treatment with venlafaxine (15 mg/kg, p.o.) counteracts these effects (Wang et al. 2011). Two studies confirm the anti-apoptotic role of venlafaxine. Indeed, in the UCMS, 28 days of venlafaxine administration (10 mg/kg, i.p.) prevents the increase of apoptotic neurons in the hippocampus (Huang et al. 2014). Moreover, Saad et al. (2019) report that after 28-day of venlafaxine treatment, ovariectomized rats exhibit a marked reduction of hippocampal Bax/Bcl2 ratio, caspase-3 activity, and tumor necrosis factor alpha levels (Saad et al. 2019).

The ability of venlafaxine to influence cell fate choice during adult neurogenesis process was also studied. For this, primary astrocyte cultures were treated with different antidepressants including venlafaxine, imipramine, and fluoxetine (Cabras et al. 2010). In the presence of each of these drugs, cultured astrocytes rapidly acquired a neuronal morphology and expressed neuronal markers. This reveals a process that might contribute to the antidepressant-like effect of venlafaxine. Several studies have shown that the response of chronic antidepressants is mediated by the stimulation of adult hippocampal neurogenesis (Hanson et al. 2011) whereas the ablation of this process attenuates the antidepressant-like effect of some antidepressants as described with SSRI and TCA (Santarelli et al. 2003; David et al. 2009). However, this proof of concept is still lacking using venlafaxine.

Impact of venlafaxine on fast-spiking interneurons extracellular matrix remodeling

Emerging evidence suggests that MDD impacts the remodeling of extracellular matrix in various brain regions. The extracellular matrix is the major constituent of perineuronal nets (PNNs) enwrapping parvalbumin (PV) expressing cells (Sorg et al. 2016), a subpopulation of GABAergic interneurons. Although the role of PNNs is not fully understood, it has been proposed that they contribute to reinforce the activation of these GABAergic interneurons, through a better sensitivity to glutamatergic inputs (Tewari et al. 2018; Frischknecht et al. 2009). As PV interneurons contact excitatory pyramidal cells in the hippocampus, PNNs significantly influence the excitatory/inhibitory (E/I) balance.

Most notably, they alter this balance (Yizhar et al. 2011), an endpoint relevant to stress-induced depressive-like state (Albrecht et al. 2016; Wang et al. 2019). In support of this assumption, an increase of PNNs has been reported in several animal models of depression such as the CSD or CORT models (Riga et al. 2017).

On the contrary, the digestion of PNNs with chondroitinase (ChABC) reduces the excitability of GABAergic interneurons (Tewari et al. 2018; Favuzzi et al. 2017) thereby increasing hippocampal activity. Interestingly, a chronic treatment with venlafaxine has been shown to reverse CORT-induced increase in PNNs as the result of an upregulation of metalloproteases (MMPs) such as MMP-9 (Bijata et al. 2017; Alaiyed et al. 2019; Alaiyed et al. 2020). MMPs are enzymes that cleave PNNs and subsequently reduce the
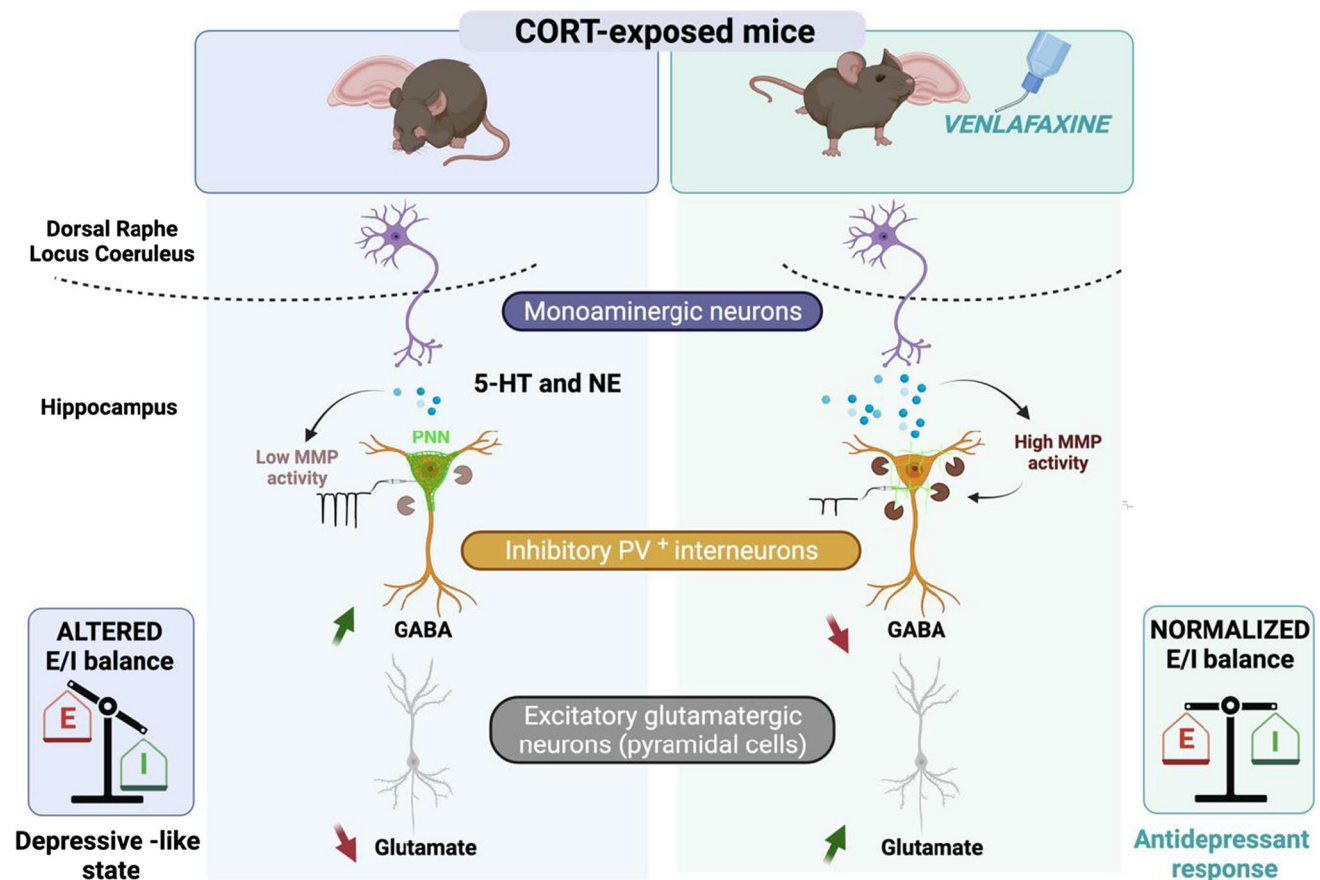

Fig. 2 Impact of venlafaxine on the excitatory/inhibitory (E/I) balance in the hippocampus. Stress increases perineuronal nets (PNNs) deposition around parvalbumin positive (PV+) GABAergic interneurons in the hippocampus due to the inactivation of metalloproteases (MMP) such as MMP9. This reinforces the excitatory synapses upon PV+ GABAergic interneurons thereby leading to their hyperactivity. Such a process would be associated to an increased release of GABA in the hippocampus. As PV+ GABAergic interneurons contact excitatory pyramidal cells, their hyperactivity induces a local inhibition of pyramidal cells. Overall altered E/I balance is observed in animal

models of depression (left panel). Venlafaxine, through the inhibition of serotonin (5-HT) and norepinephrine (NE) reuptake, promotes the accumulation of these monoamines in the synaptic cleft. Evidence demonstrates that both 5-HT and NE favor the activity of MMP9, which in turn, leads to PNNs degradation. In that condition, the activation of PV+ GABAergic interneurons is attenuated. A decreased release of GABA is then expected causing the disinhibition of pyramidal glutamatergic neurons. As a functional consequence, the E/I balance is rescued (right panel), a process necessary for antidepressant response.

activation of inhibitory PV interneurons (Bozzelli et al. 2020). As depicted in Fig. 2, a new hypothesis in the field of neuropsychopharmacology posits that venlafaxine would attenuate the PNNs which in turn would restore a normal E/I balance in CORT-exposed mice (Fig. 2). Interestingly, elevated MMP-9 levels were found in autopsy-derived prefrontal cortex samples of MDD patients treated with antidepressants compared to controls (Alaiyed et al. 2020). The involvement of MMP-9 in the regulation of emotional state is further supported by pharmacological or genetic studies showing that the inactivation of MMP-9 increases basal anxiety (Ringland et al. 2021) but also despair and sociability in stressed animals (Vafadari et al. 2019). Moreover, single nucleotide polymorphisms of MMP-9 have been unveiled in human and they have been associated with MDD (Bobińska et al. 2016a; Bobińska et al. 2016b) but also to treatment response (Rybakowski et al. 2011).

Efficacy of venlafaxine in the treatment of depressed patients

This is, now, well-established in clinics that venlafaxine is an efficient antidepressant treatment. Compared with placebo, a recent meta-analysis highlighted an odds ratio (OR) of 1.78 [95% confidence intervals (95% CI)1.61–1.96] (Cipriani et al. 2018). In the early 1990s, a number of studies compared venlafaxine with SSRIs. A first study showed a greatest improvement of depressive symptoms (Montgomery Asberg Rating Scale (MADRS) and Hamilton Depressive Rating Scale (HDRS)) in the venlafaxine group (200mg/day) versus fluoxetine (40mg/day) after 4 and 6 weeks treatment, in a population with melancholic features (Clerc et al. 1994). However, this first study focused only in 34 patients in each group. A second study compared venlafaxine 75mg (n=153) to fluoxetine 25mg (n=161). A clinical improvement was reported in the two groups, without difference between groups. There was a subgroup analysis focusing on 88 patients for which there was an increase of venlafaxine from 75mg to 150mg and so targeting both monoaminergic systems. Significant differences were described in favor of venlafaxine in the HDRS total from weeks 3 to 8 (Dierick et al. 1996). A first meta-analysis focusing on the efficacy of venlafaxine compared with SSRIs and other antidepressants highlighted that venlafaxine seemed more efficient than SSRIs. However, these results were less clear, focusing on other antidepressants such as TCAs. Moreover, this meta-analysis showed that venlafaxine carried an advantage of about 1.2 HDRS points compared with all other antidepressants (total size effect: 0.14) and even a little more, when focusing specifically on SSRIs (size effect: 0.17). This decrease seemed too small to be clinically pertinent. In addition, the NNT (number needed to treat) was of 19

(95%CI 11–63) for response and of 14 (95%CI 9–29) for remission (Smith et al. 2002). Another meta-analysis, focusing on 17 randomized controlled studies, showed a trend towards superiority of venlafaxine over SSRIs in remission rates (risk ratio [RR]= 1.07, 95%CI=0.99 to 1.15), and a slight superiority in response rates (RR=1.06, 95%CI=1.01 to 1.12) over SSRIs. However, the NNT were 34 and 27 for remission and response, respectively. There was also a modest advantage for venlafaxine in change scores (using MADRS or HDRS) (effect size=−0.09, 95% CI=−0.16 to −0.02, p=0.013) (Weinmann et al. 2008). In addition, a meta-analysis of data from 39 published and unpublished clinical trials randomized 8659 patients (n = 4644 to venlafaxine; n = 4015 to an SSRI). This meta-analysis found that venlafaxine had a higher response rate than SSRIs (RR=1.084 95% CI=1.019–1.101) (Papakostas et al. 2007). Another meta-analysis of 34 randomized, double-blind studies focusing only on remission rates, included 8744 patients (4191 patients treated with venlafaxine and 3621 treated with SSRIs). It showed that the difference in remission rates was 5.9% in favor of venlafaxine over SSRIs, as a class (95% CI= 0.038–0.081: p= 0.001). The NNT was 17 (95% CI: 12–26). Focusing on specific SSRIs, the difference from fluoxetine was significant (6.6% [95% CI: 0.030–0.095]). The difference between paroxetine, sertraline, and citalopram was not significant (Nemeroff et al. 2008). More recently, two other meta-analyses have addressed the efficacy of venlafaxine versus SSRIs. One focused on published studies. De Silva et al. noted that venlafaxine was superior to SSRIs by focusing on remission [odds ratio (OR= 1.13, 95% CI = 1.0–1.28, p = 0.05)] and response (OR = 1.17, 95% CI = 1.03–1.34, p = 0.02). In addition, venlafaxine seemed to have a significantly better response rate than fluoxetine (OR = 1.28, 95% CI = 1.05–1.55, p = 0.01). There were no significant differences in response or remission between venlafaxine and other individual SSRIs (de Silva and Hanwella 2012). The second meta-analysis included unpublished data. It showed that response rates were significantly higher for venlafaxine than for SSRIs (OR = 1.20, 95% CI 1.07–1.35). But, the remission rate was not higher for venlafaxine than for SSRIs (OR = 1.12, 95% CI 0.98–1.28) (Schueler et al. 2011). Recently, Cipriani et al. showed, in a network meta-analysis focused on comparing the efficacy of 21 antidepressant drugs for the acute treatment of adults with MDD, that fluoxetine is less effective than venlafaxine (OR= 0.84, 95% CI = 0.73–0.97) (Cipriani et al. 2018). Interestingly, a very recent meta-analysis of venlafaxine and duloxetine showed that non-RCTs (random clinical trials) are generally better suited to describe a drug efficacy in clinical practice than RCTs. However, it appears that non-RCTs are associated with a smaller size-effect than RCT (Schneider et al. 2021). In conclusion, it seems that venlafaxine is more effective than SSRIs (mainly fluoxetine which is one of the most prescribed) in terms of response

rate, despite a relatively weak size effect measured on depression scales. Interestingly, in treatment-resistant patients, it is possible to switch from SSRI to SNRI treatment like venlafaxine to observe a therapeutic response. In this way, a retrospective study showed that patients who remain severely depressed following SSRI treatment may gain benefit from a high dose of venlafaxine (i.e., 225 mg/daily) which likely improve both 5-HT and NE tone, rather than switching to another SSRI (Barak et al. 2011).

Finally, it is noteworthy that there is no evidence for the occurrence of serotonin syndrome with venlafaxine alone even in high doses. To the best of our knowledge, only one study reported that a 29-year-old depressed Taiwanese woman developed serotonin syndrome at the dose of 37.5 mg/d (Pan and Shen 2003). Several cases, however, were described when venlafaxine is combined with other pharmacological compounds including mirtazapine (Decoutere et al. 2012), tranylcypromine (Brubacher et al. 1996), fluoxetine (Bhatara et al. 1998), trazodone (McCue and Joseph 2001), or tramadol (Albiñana Pérez et al. 2012). Although the underlying mechanisms remain unknown, it is likely that the functional and reciprocal interactions between the monoaminergic systems or between 5-T/NE and the opioid system may precipitate such a syndrome.

Concluding remarks

In vitro binding studies report that venlafaxine displays a strong affinity for the human/rat SERT although a higher affinity is observed with an SSRI and a TCA (i.e., citalopram and clomipramine). Similarly, human NET/rat binding assays indicate that venlafaxine displays a good affinity for this target but to a lower extent than the NRI reboxetine (Millan et al. 2001). Compared with other SNRIs (duloxetine and levomilnacipram), venlafaxine has also less affinity for the SERT and NET transporters (Auclair et al. 2013; Béïque et al. 1998) indicating that it represents a reliable SERT and NET blocker but not the best. In vivo, electrophysiological approaches show that venlafaxine and the SSRI paroxetine share the same potency at inhibiting the SERT even though there is no direct comparison (Béïque et al. 1998). This property worth mentioning because paroxetine is recognized as the most potent SSRI currently available. However, this remarkable pharmacological property is limited to the 5HT system because studies demonstrate that several antidepressants are more potent than venlafaxine at blocking the NET. Indeed, venlafaxine is less potent at blocking the NET than reboxetine or desipramine (Auclair et al. 2013; Béïque et al. 1998). This in vivo electrophysiological profile can be compared with neurochemical studies using microdialysis. Comparing the minimal effective doses (MED)

required to increase cortical extracellular 5-HT concentrations, Millan and collaborators showed that venlafaxine has a similar profile than citalopram but is four-fold lower than that of clomipramine (Millan et al. 2001), levomilnacipran, and duloxetine (Auclair et al. 2013). As regard cortical extracellular NE concentrations, similar MED are found between venlafaxine and other SNRIs levomilnacipran and duloxetine (Auclair et al. 2013) which is quite unexpected considering the in vitro binding studies and in vivo electrophysiological data. This likely emphasizes the fact that mechanisms occurring at the nerve terminals might change our predictions regarding the net effects of venlafaxine noradrenergic neurotransmissions and behavioral properties. Indeed, in terms of behavior, only few differences were detected between antidepressants when comparing venlafaxine with the SSRIs fluoxetine, sertraline, escitalopram, and fluvoxamine; the SNRI duloxetine; the TCAs desipramine/imipramine; or other atypical antidepressants such as bupropion. Nevertheless, behavioral studies showed that venlafaxine has the lowest MED of the above-mentioned antidepressants in the TST and/or FST (Castagné et al. 2009; Socała et al. 2012). Such a difference could negatively reverberate on the onset of action of venlafaxine. In support of this hypothesis, it was shown in an animal model of depression, that the antidepressant-like effects of venlafaxine (20 mg/kg) occurred as soon as 21 days of treatment whereas a 14-day period is required with fluoxetine (20 mg/kg) to promote beneficial behavioral effects (Poretti et al. 2016). On the contrary, regarding anxiolytic response, venlafaxine is less effective than the SSRI fluoxetine or citalopram and the SNRI duloxetine when assessed in marble burying test, nestlet shredding, or zero maze (Li et al. 2006; Mirza et al. 2007)

Collectively, it appears that venlafaxine is a potent SERT inhibitor and at higher doses, is also able to block NET as NRIs do. Behavioral studies did not yield strong evidence regarding the greater effects of venlafaxine compared to the other antidepressants. With respect to clinical practice, it appears that at higher doses, thus acting as a mixed SERT/NET inhibitor, venlafaxine shows superior effects than SSRIs on response rate, but these results have yet to be confirmed. However, these potential beneficial effects are accompanied by a weaker tolerance than SSRIs, especially during the first week of treatment, thus reducing compliance and possibly attenuating its response rate (Dierick et al. 1996; Weinmann et al. 2008).

Declarations

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