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NEUROPHARMACOLOGY OF VENLAFAXINE

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Venlafaxine (Effexor) is an effective antidepressant and has also been approved for the treatment of generalized anxiety disorder. Venlafaxine was initially characterized as an inhibitor of both serotonin (5HT) and norepinephrine (NE) uptake and was therefore termed a "dual uptake inhibitor." This chapter reviews data from both in vitro and in vivo studies regarding its effects on 5HT and NE neurotransmission. In addition, the effects of venlafaxine on other systems that may play a role in its therapeutic efficacy effects are described. The data indicate that venlafaxine is a relatively weak inhibitor of NE transport in vitro. In vivo studies indicate that venlafaxine selectively inhibits 5HT uptake at low therapeutic doses and inhibits both 5HT and NE uptake at higher therapeutic doses. This chapter concludes with a discussion of the effects of venlafaxine on various aspects of physiology. Depression and Anxiety, Volume 12, Supplement 1:20–29, 2000.

Key words: ***antidepressant; antianxiety; Effexor; serotonin; norepinephrine; uptake inhibitor; SNRI***

CHEMISTRY

Venlafaxine was originally discovered in a chemical series aimed at structural modification of the mixed opiate agonist-antagonist ciramadol [Yardley et al., 1990]. Venlafaxine is a 2-phenyl-2-(1-hydroxycycloalkyl) ethylamine derivative that is chemically unrelated to tricyclic, tetracyclic or other available antidepressants (Fig. 1). It consists of a racemic mixture with the chemical designations of (R/S)-1-[2-(dimethylamino)-1-(4methoxyphenyl) ethyl] cyclohexanol hydrochloride or (±)-1-[α-[(dimethylamino)methyl]-*p*-methoxybenzyl] cyclohexanol hydrochloride. It has the empirical formula of $C_{17}H_{27}NO_2$ hydrochloride and a molecular weight of 313.87. Venlafaxine hydrochloride is an off-white crystalline solid that is highly soluble in water.

The major metabolite of venlafaxine is *O*-desmethylvenlafaxine (ODV), which is similar to venlafaxine in potency for inhibiting 5HT and NE uptake [Muth et al., 1991] and in affinity for the 5HT and NE transporters [Owens et al., 1997]. Because ODV has a longer half-life than venlafaxine, plasma concentrations of ODV exceed those of venlafaxine, and ODV most likely contributes significantly to the overall antidepressant efficacy of the drug [Klamerus et al., 1992]. The minor metabolites *N*-desmethylvenlafaxine and *N*,*O*-didesmethylvenlafaxine are much less potent at inhibiting biogenic amine uptake compared to the parent compound [Muth et al., 1991].

EFFECTS ON 5HT AND NE SYSTEMS

NEUROTRANSMITTER TRANSPORT AND RECEPTOR BINDING

Venlafaxine was identified as a potential antidepressant due to its ability to inhibit [^{3}H]imipramine binding to rat cortical membranes [Muth et al., 1986]. Subsequent studies using rat brain synaptosomes showed that venlafaxine is potent at inhibiting both 5HT and NE uptake, demonstrating a 3- to 5-fold greater potency for 5HT. In addition, it is much less potent at inhibiting dopamine (DA) uptake, demonstrating a 13- to 130-fold greater potency for 5HT [Muth et al., 1986; Bolden-Watson and Richelson, 1993]. The (+) enantiomer selectively inhibits uptake of 5HT; whereas, the (–) enantiomer is like the racemate in its potency for both 5HT and NE uptake [Muth et al., 1986]. Because of its effects on 5HT and

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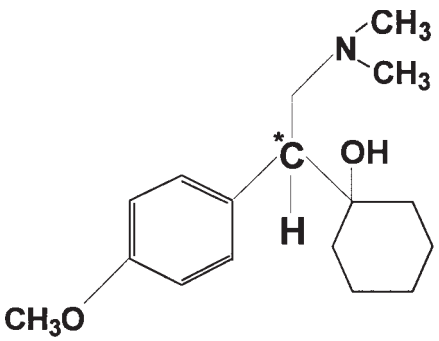

Figure 1. Structural formula of venlafaxine. The asterisk identifies the chiral center of the molecule.

NE uptake, venlafaxine has been termed a "dual uptake inhibitor." Compared to the serotonin selective reuptake inhibitors (SSRIs), venlafaxine is less potent at inhibiting 5HT uptake, and compared to the TCAs, venlafaxine is less potent at inhibiting NE uptake [Bolden-Watson and Richelson, 1993].

Venlafaxine has no significant affinity for muscarinic cholinergic, H_1-histaminergic, α_1-, α_2-, β-adrenergic, $5HT_{1A}$-, $5HT_{2A}$-serotonergic, D_2-dopaminergic and benzodiazepine receptors, and does not inhibit monoamine oxidase [Muth et al., 1986; Cusack et al., 1994; Owens et al., 1997]. Therefore it should not have the adverse effects of the tricyclic antidepressants (TCA).

More recent studies suggest that venlafaxine has much less activity against the NE transporter than previously described. Venlafaxine inhibited uptake of 5HT and NE in cells transfected with either the cloned human 5HT or NE transporters with K_is of 0.102 μM and 1.6 μM, respectively; the values for the active metabolite ODV were similar. This represents a 16-fold lower potency for inhibiting NE uptake [Owens et al., 1997]. In addition, other studies measuring the ability of venlafaxine to inhibit radioligand binding to the rat and human 5HT and NE transporters reported a 17- to 300-fold lower affinity for the NE transporter compared to the serotonin transporter [Owens et al., 1997; Tatsumi et al., 1997; Beique et al., 1998b].

The recent in vitro studies have led some to recharacterize venlafaxine as an SSRI [Tatsumi et al., 1997]. However, this conflicts with in vivo data that indicate the ability of venlafaxine to inhibit 5HT and NE uptake is similar. Additionally, it is important to note that the plasma concentration of venlafaxine plus ODV that is associated with antidepressant efficacy is sufficient to partially inhibit NE transport. The maximal concentrations achieved for the sum of venlafaxine and ODV with three different daily doses of venlafaxine are as follows: 75 mg/0.6 μM, 225 mg/1.8 μM and 450 mg/3.4 μM [Klamerus et al., 1992]. Because plasma protein binding is only 20–30% for venlafaxine, these data suggest that concentrations in the brain would be in the range of 1.6 μM, which is the K_i for inhibition of transport of the cloned human NE transporter [Owens et al., 1997].

ELECTROPHYSIOLOGY

The ability of a drug to inhibit the firing of serotonergic neurons in the dorsal raphe nucleus (DRN) and noradrenergic neurons in the locus ceruleus (LC) is used as an indication of its ability to increase extracellular levels of 5HT and NE, respectively [Quinaux et al., 1982]. The effect on serotonergic neurons in the DRN is likely mediated by somatodendritic $5HT_{1A}$ autoreceptors because it is blocked by the $5HT_{1A}$ autoreceptor antagonist WAY100635 [Gartside et al., 1995]. The effect on noradrenergic neurons in the LC is likely mediated by α_2-adrenergic autoreceptors because it is blocked by the α_2-adrenergic receptor antagonist piperoxan [Beique et al., 1999].

Electrophysiological studies performed with venlafaxine are consistent with dual 5HT and NE uptake inhibition. Venlafaxine was as potent as the SSRI paroxetine at inhibiting the firing of serotonergic neurons in the DRN. The effects of venlafaxine were completely reversed by WAY 100635 [Gartside et al., 1997; Beique et al., 1999]. Venlafaxine inhibited the firing of noradrenergic neurons in the LC, but was 3-fold less potent than the selective NE uptake blocker desipramine. The effects of venlafaxine were reversed by piperoxan [Haskins et al., 1985; Beique et al., 1999]. Direct comparison of the two paradigms reveals that venlafaxine is three-fold more potent at inhibiting the firing of serotonergic neurons in the DRN than inhibiting the firing of noradrenergic neurons in the LC [Beique et al., 1999]. This is consistent with uptake studies that indicate that venlafaxine is slightly more potent at inhibiting the uptake of 5HT than NE [Muth et al., 1986; Bolden-Watson and Richelson, 1993].

Results similar to those for the DRN and LC have been reported for the dorsal hippocampus. Intravenously administered venlafaxine prolonged the time required for a 50% recovery of firing activity of CA3 pyramidal neurons following suppression of activity induced by iontophoretically applied 5HT or NE [Beique et al., 1998a]. This effect likely results from venlafaxine blocking the neuronal uptake of the applied 5-HT and NE and thereby prolonging their inhibitory effects on the pyramidal neurons. Venlafaxine was more potent at prolonging recovery time after 5HT treatment than NE treatment. Venlafaxine and paroxetine increased the recovery time after 5HT treatment with a similar potency; whereas, venlafaxine was 3-fold less potent than desipramine at increasing the recovery time after NE treatment.

It is also possible for drugs that block the uptake of NE to stimulate the release of 5HT in the DRN through activation of somatodendritic α_1-adrenergic receptors located on serotonergic neurons. Theoretically, NE acting on stimulatory α_1-adrenergic receptors could antagonize the inhibitory effects of 5HT

acting on $5HT_{1A}$ autoreceptors. Therefore a mixed acting 5HT/NE uptake blocker may be less potent at inhibiting the firing of serotonergic DRN neurons. The fact that venlafaxine is equipotent with the SSRI paroxetine, indicates that if venlafaxine does increase NE in the DRN, the effects of activating the α_1-adrenergic receptors seem to be insufficient to overcome the inhibitory actions of 5HT on the $5HT_{1A}$ autoreceptors.

The above electrophysiological data in rats suggest that venlafaxine has a modest selectivity for inhibiting 5HT vs. NE uptake. This agrees with earlier studies on the effects of venlafaxine on the uptake of 5HT and NE into rat brain synaptosomes [Muth et al., 1986; Bolden-Watson and Richelson, 1993]. In contrast, these data differ from the recent in vitro radioligand binding studies on rat cortex 5HT and NE transporters that predict that venlafaxine should have a 56-fold greater potency at inhibiting 5HT vs. NE uptake [Owens et al., 1997]. This suggests that inhibiting 5HT and NE transport, and ultimately inhibiting 5HT and NE neuronal firing, require steps in addition to binding to the transporter.

Another discrepancy is apparent when comparing the electrophysiological effects of venlafaxine to other antidepressants. Based on in vitro transport and radioligand binding studies in the rat, venlafaxine should be at least 50-fold less potent than paroxetine at inhibiting 5HT transport and, therefore, at inhibiting 5HT neuronal firing in the rat DRN [Owens et al., 1997]. In contrast, venlafaxine and paroxetine are equipotent at inhibiting the firing of 5HT neurons. Only a portion of the greater than expected potency of venlafaxine in the in vivo studies can be accounted by the low plasma protein binding of venlafaxine compared to paroxetine. Another possible explanation is that the dual uptake inhibition produced by venlafaxine could result in interactions between the 5HT system in the DRN and the NE system in LC. Lesioning studies, however, suggest this is not the case. In addition, because venlafaxine is a phenylethylamine derivative, and therefore related to amphetamine, it is possible it could be stimulating 5HT or NE release. However, this was shown not to occur with venlafaxine [Beique et al., 1999]. Therefore, the ability of venlafaxine to inhibit neuronal firing may involve mechanisms in addition to its effects on the 5HT and NE transporters.

IN VIVO MICRODIALYSIS

Acute studies. Several studies have used in vivo microdialysis to determine the effects of venlafaxine on the extracellular concentrations of 5HT and NE. The frontal cortex receives serotonergic projections from the DRN. The effects of venlafaxine on the extracellular concentration of 5HT in the frontal cortex are consistent with its effects on the firing of serotonergic neurons in the DRN. In two separate studies, venlafaxine increased the extracellular levels of 5HT in the frontal cortex [Gur et al., 1999; Hatanaka et al., 2000b]. One study failed to report an increase in 5HT levels in the frontal cortex when venlafaxine was given alone, but found a significant increase in 5HT in the presence of the $5HT_{1A}$ receptor antagonist, WAY-100635 [Dawson et al., 1999]. This likely results from WAY100635 preventing 5HT inhibition of neuronal firing through somatodendritic $5HT_{1A}$ autoreceptors in the DRN, as reported in the electrophysiological studies described in the previous section [Gartside et al., 1997; Beique et al., 1999]. Additionally, in the presence of the $5HT_{1B/D}$ receptor antagonist GR-127935, the venlafaxine/WAY100635 combination gave a significantly larger increase in frontal cortex 5HT levels, suggesting that presynaptic $5HT_{1B/D}$ receptors also have an inhibitory effect on the firing of DRN serotonergic neurons [Dawson et al., 1999].

Administration of venlafaxine produced a more dramatic increase in extracellular 5HT in the hippocampus compared to the frontal cortex. This effect was augmented by the mixed β-adrenergic/$5HT_{1A}$ antagonist pindolol [Gur et al., 1999]. The difference in the magnitude of the response between the two brain regions may be due in part to the higher density of 5HT uptake sites present in the hippocampus [Hrdina et al., 1990]. In addition, there is a lower density of somatodendritic $5HT_{1A}$ autoreceptors present in the median raphe, which innervates the hippocampus compared to the dorsal raphe, which innervates the frontal cortex.

The effects of venlafaxine on extracellular levels of NE in the frontal cortex are also consistent with its effects on the firing of noradrenergic neurons in the LC. Venlafaxine significantly increased the extracellular levels of NE in the frontal cortex [Dawson et al., 1999; Hatanaka et al., 2000a], and this effect was augmented by the α_2-adrenergic autoreceptor antagonist idazoxane [Dawson et al., 1999]. This indicates that α_2-adrenergic autoreceptors are activated by venlafaxine-induced increases in extracellular NE.

Under the appropriate conditions it is also possible to demonstrate that the venlafaxine-induced inhibition of NE uptake affects extracellular 5HT levels. As mentioned above, NE can have a stimulatory effect on serotonergic neurons in the DRN by activating somatodendritic α_1-adrenergic receptors located on serotonergic neurons. Administration of the α_1-adrenergic receptor antagonist prazosin significantly attenuated the venlafaxine/WAY100635-induced increase in extracellular 5HT levels in the frontal cortex [Dawson et al., 1999]. Additionally, administration of the α_2-adrenergic autoreceptor antagonist idazoxane significantly augmented the venlafaxine/WAY100635-induced increase in extracellular 5HT. This could result from the blockade of the inhibitory effect of NE on presynaptic α_2-adrenergic heteroreceptors on serotonergic neurons or from the stimulatory effect of NE on somatodendritic α_1-adrenergic receptor on serotonergic neurons. None of these adrenergic effects on 5HT levels were seen in the absence of WAY100635. This indicates that the dominant regulator of serotonergic neuronal activity

is 5HT acting on the $5HT_{1A}$ receptor. Only when this pathway is inhibited by WAY100635, is it possible to unmask the effects of α_1- and α_2-adrenergic receptors on serotonergic neurotransmission.

Chronic studies. Several studies have reported that chronic administration of various 5HT and NE uptake inhibitors elevates the basal extracellular levels of these neurotransmitters in various brain regions [Bel and Artigas, 1993, 1996; Rutter et al., 1994; Auerbach and Hjorth, 1995; Kreiss and Lucki, 1995; Tanda et al., 1996]. This increase has been ascribed to a desensitization of $5HT_{1A}$ and $5HT_{1B}$ autoreceptors, and this effect has been demonstrated in several studies [Invernizzi et al., 1994; Rutter et al., 1994; Kreiss and Lucki, 1995]. In contrast, other studies have failed to demonstrate changes in basal neurotransmitter levels [Sleight et al., 1989; Hjorth and Auerbach, 1994; Bosker et al., 1995a, 1995b; Invernizzi et al., 1995, 1996; Kihara and Ikeda, 1995; Arborelius et al., 1996; Moret and Briley, 1996; Gundlah et al., 1997] or a desensitization of $5HT_{1A}$ and $5HT_{1B}$ autoreceptors [Hjorth and Auerbach, 1994; Bosker et al., 1995b; Invernizzi et al., 1995; Gur et al., 1999]. To date the only chronic study preformed with venlafaxine showed no effect of 4 weeks of daily injections on basal levels of extracellular 5HT in the frontal cortex or hippocampus, and did not demonstrate a desensitization of $5HT_{1A}$ autoreceptors [Gur et al., 1999]. Clearly, more studies are required to define the effects of chronic venlafaxine on the serotonergic and noradrenergic systems.

ANIMAL MODELS OF ANTIDEPRESSANT ACTIVITY

The ability of venlafaxine to inhibit uptake of either 5HT or NE presumably accounts for its activity in several in vivo models that are sensitive to antidepressants. Venlafaxine reversed reserpine-induced hypothermia in CF-1 mice, which is a test thought to involve effects on the noradrenergic system [Yardley et al., 1990]. Venlafaxine was also active in a test of behavioral despair, the mouse forced swimming test, without producing either sedation or stimulation [Lloyd et al., 1992]. In another study, venlafaxine was active in the forced swimming test but also increased locomotor activity at all but the lowest dose tested. The authors concluded that venlafaxine was acting through inhibition of 5HT uptake at lower doses and through inhibition of both 5HT and NE uptake at higher doses [Redrobe et al., 1998]. In addition, this group showed that venlafaxine reversed the hypothermia produced by high dose apomorphine, which is an effect seen with antidepressants that inhibit NE uptake. Venlafaxine did not block the stereotyped behavior that results from high dose apomorphine acting through DA receptors, which indicates that venlafaxine does not have antidopaminergic activity.

Only one study examined the effects of venlafaxine in the forced swimming test using rats. In this study, venlafaxine produced a dose-dependent decrease in immobility, similar to results reported with mice. Examination of the active behaviors produced in the forced swimming test revealed that venlafaxine increased swimming behavior at all doses tested and also increased climbing behavior only at the highest dose tested. The effects on swimming behavior are consistent with venlafaxine acting on both 5HT and NE uptake. The observation that the highest dose of venlafaxine increased both climbing and swimming behavior suggests that at this dose, it may have effects on dopaminergic neurotransmission [Reneric and Lucki, 1998]. This would be consistent with uptake studies that reveal that venlafaxine has weak activity at inhibiting the uptake of DA into rat synaptosomes [Muth et al., 1986].

Venlafaxine has effects similar to other antidepressants in the resident-intruder social interaction paradigm. Acute treatment of resident rats with venlafaxine reduced aggressive behavior toward the unfamiliar intruder rat with a concomitant increase in flight-escape behavior. In contrast, constant infusion of venlafaxine for 7 or 14 days increased aggressive behavior toward the intruder with a concomitant decrease in the flight-escape behavior [Mitchell and Fletcher, 1993]. The diametrically opposed effects of acute vs. chronic drug administration in this paradigm are consistent with the responses seen for a wide variety of structurally unrelated antidepressants [Mitchell and Redfern, 1992].

HUMAN STUDIES

To determine the effects of venlafaxine on 5HT and NE neurotransmission in vivo in humans various peripheral measures can be taken. On the whole, these studies suggest that venlafaxine affects both 5HT and NE uptake at the higher doses used clinically.

To compare the ability of venlafaxine to inhibit 5HT and NE transport in vivo, uptake of 5HT into platelets is used as a measure of 5HT transporter activity and the pressor response to intravenous tyramine is used as a measure of NE transporter activity. In the latter response, tyramine enters noradrenergic nerve terminals via the NE transporter, displaces NE from intracellular stores, and that leads to NE release and a transient increase in blood pressure. In healthy male volunteers both 75 mg and 375 mg doses of venlafaxine administered daily for 15 days significantly inhibited the uptake of 5HT into platelets. In contrast, only the high dose of venlafaxine inhibited the pressor response to tyramine [Harvey et al., 2000]. This study provides in vivo evidence that in humans, at clinically relevant concentrations, venlafaxine sequentially affects 5HT and NE neurotransmission presumably by inhibiting the uptake of 5HT and NE. A limitation of this study is that peripheral and not brain measures were used to determine effects on 5HT and NE function.

Another method used to demonstrate the ability of venlafaxine to inhibit NE uptake in vivo in humans is to measure the potentiation of NE-induced venoconstriction of the dorsal hand vein [Aellig, 1981]. A

single oral dose of 150 mg venlafaxine, but not 75 mg, given to healthy human volunteers potentiated the ability of locally infused NE to produce venoconstriction of the dorsal hand vein [Abdelmawla et al., 1999]. In the same paradigm, venlafaxine did not alter the venoconstrictor effects of methoxamine, an α_1-adrenergic agonist that is not subject to neuronal uptake. A single oral dose of 100 mg desipramine, a TCA with NE uptake blocking properties, produced effects similar to 150 mg of venlafaxine. In contrast, placebo or 20 mg of the SSRI, paroxetine, were without effect on venoconstrictor responses. These results indicate that clinically relevant single doses (150 mg) of venlafaxine inhibit NE uptake in the periphery in humans. The observation that 75 mg of venlafaxine was without effect suggests that tissue concentrations achieved with this dose are not sufficient to affect uptake of exogenously administered NE. This is consistent with the greater potency of venlafaxine for inhibiting the uptake of 5HT over NE, which suggests that at lower doses venlafaxine may selectively inhibit 5HT uptake. It should be noted that in this study venlafaxine by itself slightly elevated blood pressure, an effect that may reflect NE uptake blockade leading to sympathetic potentiation. The effects of venlafaxine on the cardiovascular system are described in more detail later in this review.

The human pupil is also used as a non-invasive system to test noradrenergic responses in vivo. Drug-induced pupil dilatation (mydriasis) can result from an increase in sympathetic (noradrenergic) or a decrease in parasympathetic (cholinergic) influences on the iris. Systemic administration of 75 or 150 mg venlafaxine to 15 healthy male volunteers produced a significant mydriasis [Bitsios et al., 1999]. Because venlafaxine has no affinity for muscarinic cholinergic receptors, venlafaxine-induced mydriasis most likely results from inhibition of NE uptake that potentiates the effects of the sympathetic input on the iris. These effects of venlafaxine are most likely not mediated through inhibition of 5HT uptake because in the same experiment, the SSRI paroxetine did not have an effect on resting pupil diameter.

The time course of the pupillary light reflex is also influenced by the relative amount of sympathetic versus parasympathetic tone. The latency and the amplitude of the response are under control of the parasympathetic system and the recovery is under control of the sympathetic system. Venlafaxine significantly increased the latency, decreased the amplitude and shortened the recovery time of the pupillary light reflex [Bitsios et al., 1999]. The SSRI paroxetine was without effect on these three aspects of the reflex. The effects of venlafaxine on recovery time are consistent with its potentiation of the effects of NE on the iris. In contrast, the effects of venlafaxine on the latency and amplitude are surprising because these effects are usually associated with parasympathetic inhibition. These responses may result from potentiation of the inhibitory effects of NE on parasympathetic neurons in the Edinger-Westphal nucleus, which would result in a "pseudo-anticholinergic" effect on the pupillary light reflex. Therefore, the effects of venlafaxine on the pupil are consistent with inhibition of NE uptake in vivo.

EFFECTS ON OTHER SYSTEMS

β-ADRENERGIC RECEPTOR-COUPLED ADENYLATE CYCLASE

Chronic but not acute administration of antidepressants desensitizes the β-adrenergic receptor-coupled adenylate cyclase system (βAR-AC) in the rat brain, and this is often associated with a downregulation of β-adrenergic receptors [Mobley and Sulser, 1981]. This effect is seen most consistently with antidepressants that inhibit NE uptake and less consistently with antidepressants that selectively inhibit 5HT uptake. Surprisingly, twice daily injections of venlafaxine for either 10 or 14 days failed to desensitize the βAR-AC or alter the density of β-adrenergic receptors in the rat cortex [Yardley et al., 1990; Nalepa et al., 1998]. Venlafaxine, however, was able to desensitize this system in rat brains depleted of 5HT by p-chlorophenylalanine pretreatment [Nalepa et al., 1998]. This study points to a possible interaction between the NE and 5HT receptor systems in the antidepressant-induced desensitization of the βAR-AC response.

Chronic antidepressant treatment has also been shown to desensitize the βAR-AC system and downregulate β-adrenergic receptors in the rat pineal gland [Moyer et al., 1979; Moyer et al., 1981; Cowen et al., 1983]. Pineal melatonin synthesis is under the control of NE released onto pineal adrenergic receptors [Klein et al., 1970]. The desensitization and downregulation most likely results from the inhibition of NE uptake, which increases the extracellular level of NE in the pineal gland. In contrast to effects in the cortex, venlafaxine and its major metabolite ODV were able to desensitize the βAR-AC after either single or repeated administration in the rat [Yardley et al., 1990; Muth et al., 1991; Franklin et al., 1998]. This early venlafaxine-induced desensitization of the pineal βAR-AC system has been suggested by some to be related to the purported earlier onset of clinical response seen with venlafaxine [Montgomery, 1995; Rickels et al., 1995].

CA^{++}/CAM-DEPENDENT PROTEIN KINASE II

Long-term treatment of rats with antidepressants has been shown to increase neurotransmission in projections from the raphe nucleus. In the case of serotonergic neurons this is thought to result from an increase in the release of 5HT from presynaptic terminals produced by a desensitization of 5HT presynaptic autoreceptors [Kreiss and Lucki, 1995]. Ca^{2+}/calmodulin-dependent protein kinase II is involved in the machinery that regulates neurotransmitter release. Long-term treatment with venlafaxine increased Ca^{2+}/calmodulin-dependent protein kinase II activity and

autophosphorylation in the hippocampus [Popoli et al., 1995]. Similar effects were also seen with the SSRIs paroxetine and fluvoxamine. The effect seemed to be selective for the presynaptic vs. postsynaptic kinase activity. Further studies are required to determine to what extent this increase in kinase activity is involved in the therapeutic efficacy of venlafaxine.

CORTICOTROPIN RELEASING FACTOR

Corticotropin releasing factor (CRF) is a 41 amino acid peptide that integrates the endocrine, autonomic and behavioral responses to stress. Administration of CRF in the brain produces somatic changes in animals that are analogous to those observed in depression and anxiety. Levels of CRF are elevated in the cerebrospinal fluid (CSF) of depressed patients, and effective antidepressant treatments decrease the levels of CRF in the CSF [Veith et al., 1993; Mitchell, 1998; Arborelius et al., 1999]. To date little has been reported on the effects of venlafaxine on the CRF system. In a recent study, rhesus monkeys (N = 12) received vehicle or 15 mg/kg oral venlafaxine daily for 17 days. Baseline testing was done prior to the start of treatment and again on Days 15–17. Venlafaxine treatment lowered the activity of the brain CRF system as evidenced by a 21% decrease in the levels of CRF in the CSF ($P < 0.02$); however, it had no effect on plasma cortisol or ACTH levels [Kalin and Shelton, unpublished data]. These data indicate that venlafaxine produces effects on the CRF system that are consistent with those reported for other antidepressants.

EFFECTS ON PHYSIOLOGY

SLEEP

Most antidepressants alter sleep patterns and in general reduce or suppress REM sleep time. Venlafaxine seems to be similar to other antidepressants in this regard. In rats, venlafaxine produced a dose-related suppression of REM sleep, reduced the duration of slow wave sleep and increased wake time [Salin-Pascual and Moro-Lopez, 1997]. In humans, treatment of patients suffering from major depression with venlafaxine reduced sleep continuity, which was seen as an increase in wake duration after sleep onset. Total sleep time was decreased and wake time was increased. It also increased the onset latency for REM sleep and decreased total REM sleep time. These effects were seen after 1 week of treatment and were still present after 1 month of treatment. A similar reduction in REM sleep was seen in non-depressed volunteers treated with venlafaxine [Luthringer et al., 1996].

CENTRAL NERVOUS SYSTEM

In normal subjects electroencephalogram (EEG) recordings were assessed after a single oral dose of placebo, 12.5 mg, 25 mg, or 50 mg venlafaxine. Venlafaxine produced a significant decrease in absolute power, that was associated with an increase in the delta/theta and beta activity and a decrease in alpha activity [Saletu et al., 1992]. Differing from the effects of acute treatment, chronic treatment with venlafaxine in rhesus monkeys (15 mg/kg/day) resulted in increased alpha EEG activity (8–12 Hz band) in the frontal and parietal regions [Kalin, Shelton and Davidson, unpublished data]. In humans, acute venlafaxine treatment was also associated with a dose-dependent improvement in attention, concentration, memory, fine motor activity, reaction time performance and wakefulness [Saletu et al., 1992]. These effects of venlafaxine were similar to those seen with the TCA, imipramine. In the same study, venlafaxine treatment did not affect cognitive event related potentials, eye blink rate or mood compared to placebo [Semlitsch et al., 1993]. These studies indicate that acute venlafaxine treatment has effects on cognitive information processing, but how these acute effects relate to the effects of therapeutic dosing regimens has yet to be determined.

In a preliminary study, functional magnetic resonance imaging (fMRI) techniques were used to image the brains of two control and two depressed subjects at baseline and again two weeks later. The depressed patients were treated with venlafaxine after the baseline scan. Echo-planar imaging was used to acquire whole brain images while subjects viewed positively and negatively valenced visual stimuli. For both groups the negative stimuli produced a greater global activation that decreased from the baseline scan to the two-week scan. A similar decrease in activation was seen in the control subjects when exposed to positive stimuli. In contrast, when depressed subjects were shown positive stimuli they showed no activation at baseline. At the two week scan, however, an area of activation emerged in the right secondary visual cortex [Kalin et al., 1997]. These preliminary studies suggest that venlafaxine has effects on emotional processing that can be monitored by fMRI. The extent to which these effects are involved in the therapeutic response to venlafaxine remains to be established.

CARDIOVASCULAR

Venlafaxine has been associated with modest sustained increases in blood pressure, that are most likely related to the inhibition of central NE uptake. In a pool of 2,897 patients treated for depression, a sustained elevation in blood pressure was defined as a supine diastolic blood pressure reading of 90 mm Hg or higher concomitant with an increase of 10 mm Hg or higher above baseline for three consecutive recordings. For patients receiving daily doses of venlafaxine below 100 mg for 6 weeks, the chance of having a sustained increase in blood pressure was no greater than placebo. For patients receiving higher daily doses of venlafaxine up to 300 mg, the chance of having a sustained blood pressure elevation was 3 to 4% higher than that of placebo-treated patients, and for patients receiving >300 mg the chance was 11% higher than

that of placebo-treated patients [Rudolph and Derivan, 1996]. For half of the venlafaxine-treated patients that had sustained blood pressure increases, their blood pressure readings declined below the definition for sustained blood pressure elevation during continued venlafaxine treatment. In this study, the increase in risk for sustained increase in blood pressure was similar to that seen with the TCA imipramine. In addition, two other studies comparing the effects of venlafaxine (150 to 375 mg/day) and imipramine (200 or 225 mg/day) on blood pressure found no significant difference between the two agents [Ferguson et al., 1994; Grunder et al., 1996].

In the pool of 2,897 patients, heart rate was also increased significantly in venlafaxine-treated patients by approximately 3 beats/min, but there was no indication of serious arrhythmias or significant prolongation of the mean PR, QRS and QT_c intervals [Rudolph and Derivan, 1996].

Drug overdose with venlafaxine in humans has been associated with hypotension and sinus tachycardia [Peano et al., 1997; Rosen et al., 1997]. In addition, widening of the QRS interval has been seen in some patients [Kokan and Dart, 1996]. There have been only a few reports of death associated with venlafaxine overdose and the mechanisms underlying these fatalities are unclear [Parsons et al., 1996; Jaffe et al., 1999]. To understand the cardiovascular properties of venlafaxine, Khalifa et al. [1999] examined its effects on the inward I_{Na} current, which is the major depolarizing current involved in impulse propagation within the ventricles. Studies were performed on guinea pig cardiac myocytes using a whole-cell, voltage-clamp configuration of the patch-clamp technique. Venlafaxine was a potent blocker of the I_{Na}. The block did not change with hyperpolarization and seemed to be produced in a use-independent manner. This suggest venlafaxine binds to the resting state of the channel [Khalifa et al., 1999]. This effect differs from that produced by TCAs and other class I antiarrhythmic drugs, that produce both tonic and use-dependent inhibition of the I_{Na} [Krafte et al., 1994].

NEUROENDOCRINE

In humans, intravenous administration of L-tryptophan leads to an increase in growth hormone (GH) levels in the blood. This response is thought to be mediated through activation of postsynaptic $5HT_{1A}$ receptors, and is used as a measure of $5HT_{1A}$ receptor function in vivo. The GH response to L-tryptophan is consistently blunted in depressive illness [Power and Cowen, 1992] and seems to recover after successful treatment [Upadhyaya et al., 1991]. In healthy subjects, acute administration of the TCA, clomipramine, increases the GH response to L-tryptophan [Anderson and Cowen, 1986]. Likewise, administration of 18.75 mg of venlafaxine to 12 healthy male volunteers 3 hr before infusion of L-tryptophan significantly enhanced the GH response compared to pretreatment with placebo [Porter et al., 1999]. These results are consistent with venlafaxine acting to enhance serotonergic neurotransmission through $5HT_{1A}$ postsynaptic receptors. However, α_2-adrenergic receptors have been shown to regulate GH release [Siever and Uhde, 1984], the possibility exists that the effects of venlafaxine on GH levels result from inhibition of NE uptake, which leads to activation of α_2-adrenergic receptors. This seems unlikely, however, given the low dose of venlafaxine that was used in this study that would be expected to only affect the uptake of 5HT.

Acute administration of inhibitors of either 5HT or NE uptake can increase plasma cortisol levels in humans [Laakmann et al., 1984]. This is in contrast to the effects of chronic administration of antidepressants, which tends to decrease the hypercortisolemia associated with depression [Arborelius et al., 1999]. In a study involving 6 healthy male subjects, venlafaxine produced a dose-dependent increase in plasma cortisol levels 2–3 hr after a single dose [Daffner-Bugia et al., 1996]. These results are consistent with venlafaxine inhibiting the uptake of 5HT and NE in vivo. It is unlikely that this acute effect on the HPA axis participates in the therapeutic efficacy of antidepressants.

PAIN

For many years TCAs have been used to treat severe pain in non-depressed patients [Spiegel et al., 1983; Tura and Tura, 1990]. Because venlafaxine shares some characteristics with the TCAs, its usefulness in the treatment of severe pain has been investigated. There are some reports of venlafaxine producing analgesia in humans suffering from various forms of pain [Songer and Schulte, 1996; Dwight et al., 1998; Davis and Smith, 1999]. In preclinical studies using the mouse hotplate test, venlafaxine produced a dose dependent analgesia with an EC_{50} of 46.7 mg/kg [Schreiber et al., 1999]. These effects were blocked by opiate receptor antagonists, suggesting that venlafaxine-induced analgesia is opiate mediated. In another study, venlafaxine was shown to reduce thermal hyperalgesia in rats with experimental mononeuropathy [Lang et al., 1996]. At this point more studies are required to determine if venlafaxine could be a useful analgesic.

SUMMARY

Venlafaxine is a structurally novel antidepressant that selectively blocks neurotransmitter uptake without having a significant affinity for a wide variety of neurotransmitter receptors. This most likely accounts for its low side effect profile. The ability of venlafaxine to affect 5HT and NE neurotransmission has been demonstrated in a wide variety of in vitro and in vivo systems. Recent pharmacological data indicates that venlafaxine and its active metabolite ODV are at least an order of magnitude less potent at inhibiting NE vs. 5HT uptake. Nevertheless, human plasma concentration data indicate that the blood levels asso-

ciated with antidepressant efficacy would predominantly affect 5HT transport at low therapeutic doses and both 5HT and NE transport at high therapeutic doses. The recruitment of NE at higher doses is also evident in the side effect profile at the higher doses, which resembles that associated with NE uptake inhibitors (i.e., elevation of blood pressure).

More studies are required to define the exact mechanism by which venlafaxine produces its antidepressant action. High dose venlafaxine therapy has been purported to produce a faster therapeutic response compared to other antidepressants [Rickels et al., 1995], and the underlying mechanism for this is controversial [Frazer, 1997]. The extent to which the inhibition of both 5HT and NE uptake contributes to this remains to be determined. To date little has been done to define the long-term changes that result from venlafaxine-induced inhibition of 5HT and NE uptake. By describing the effects of chronic venlafaxine treatment on gene expression it may be possible to identify additional targets for even more selective psychopharmacologic agents. Finally, because venlafaxine is very selective in its actions on neurotransmitter uptake without interacting with neurotransmitter receptors, it can be a useful experimental tool to further elucidate the roles of 5HT and NE in normal brain function.

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