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ORIGINAL INVESTIGATION

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Comparison of the effects of venlafaxine, paroxetine and desipramine on the pupillary light reflex in man

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Abstract *Rationale:* The time-course of the pupillary light reflex response is determined by the successive activation of the parasympathetic and sympathetic innervations of the iris, the latency and the amplitude reflecting parasympathetic and the recovery time mainly sympathetic activity. *Objective:* To compare the effects of single doses of three antidepressants (venlafaxine: serotonin/noradrenaline reuptake inhibitor, paroxetine: selective serotonin reuptake inhibitor, and desipramine: tricyclic antidepressant) on resting pupil diameter and the pupillary light reflex response. *Methods:* Fifteen healthy male volunteers participated in five weekly sessions, each of which was associated with one treatment (venlafaxine 75 mg or 150 mg, paroxetine 20 mg, desipramine 100 mg, or placebo) according to a double-blind, double-dummy, balanced, cross-over design. An infrared binocular television pupillometer was used for the recording of the resting pupil diameter and the pupillary light reflex in darkness, in previously dark-adapted eyes. Resting pupil diameter in darkness was recorded before and after treatment. The pupillary light reflex was elicited after treatment, with six light flashes (green, 565 nm peak wavelength) of 200 ms duration and of incremental illuminance (measured in the plane of the cornea): 3.0×10^{-3}, 8.5×10^{-3}, 2.5×10^{-2}, 7.0×10^{-2}, 0.18, 0.43 mW cm^{-2}. The parameters studied were: latency, amplitude and 75% recovery time. *Results:* Analyses of variance followed by post hoc tests (least significant difference test or Dunnett's test; $P < 0.05$) revealed that both doses of venlafaxine produced a significant increase in resting pupil diameter, decrease in amplitude and shortening of the 75% recovery time of the light reflex response; venlafaxine 150 mg prolonged the latency, while the other treatments had no significant effects. *Conclusions:* The increase in resting pupil diameter could be indicative of parasympathetic inhibition and/or sympathetic activation. The shortening of the recovery time of the light reflex response is consistent with sympathetic potentiation resulting from noradrenaline uptake blockade in the iris. The prolongation of the latency and decrease of the amplitude of the light reflex response are indicative of a parasympatholytic effect of venlafaxine. However, as venlafaxine has negligible affinity for muscarinic cholinoceptors, this effect cannot be attributed to the blockade of cholinoceptors in the iris. A possible explanation for this finding is that it reflects a central rather than a peripheral effect of the drug: the blockade of noradrenaline uptake in the brain could lead to the potentiation of the noradrenergic inhibition of central parasympathetic (Edinger-Westphal) neurones. These results demonstrate the ability of therapeutically relevant single doses of venlafaxine to potentiate noradrenergic responses in man, consistent with the blockade of noradrenaline uptake.

Key words Light reflex · Pupil · Venlafaxine · Paroxetine · Desipramine · Human volunteers

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Introduction

Venlafaxine is an antidepressant with serotonin and noradrenaline uptake inhibiting properties (SNRI) with a weak effect on dopamine uptake (Muth et al. 1986; Bolden-Watson and Richelson 1993). Venlafaxine does not inhibit monoamine oxidase A or B (Muth et al. 1986) and does not have anticholinergic, antiadrenergic, antiserotonergic or antihistaminergic properties (Preskorn 1994). It is believed that at lower doses venlafaxine acts mainly as a serotonin re-uptake inhibitor, whereas at higher doses, it exerts an additional noradrenergic re-uptake inhibition (Muth

et al. 1986; Richelson 1994). The latter has been thought to account for venlafaxine's increased efficacy in severely depressed patients when higher doses are used (DeMontigny and Preskorn 1995; Preskorn 1995).

There is little evidence, however, that venlafaxine inhibits noradrenaline re-uptake at clinically used doses in humans, or that noradrenergic uptake blockade occurs mainly at the upper limits of the recommended dosage range. In a recent single dose study, venlafaxine 150 mg, but not venlafaxine 75 mg, potentiated the venoconstrictor response to noradrenaline in healthy volunteers, consistent with the postulated noradrenergic re-uptake inhibiting effect of the drug at higher dosage levels (Abdelmawla et al. 1997a).

The human pupil is a suitable, non-invasive system to test noradrenergic responses in humans, in vivo. Mydriasis evoked by systemically administered drugs may be the result of increased sympathetic or reduced parasympathetic influence on the iris, or both, and drug-induced miosis may be the result of decreased sympathetic or increased parasympathetic influence on the iris, or both. The pupillary light reflex response (see Fig. 1.) may help to elucidate the effects of a drug on the sympathetic and parasympathetic inputs to the iris, since the time-course of the light reflex response is determined by the successive activation of the parasympathetic and sympathetic inputs, latency and amplitude reflecting parasympathetic activation, and recovery time reflecting mainly sympathetic activation (Loewenfeld 1993).

The aim of this study was to provide evidence for the noradrenaline re-uptake inhibiting property of venlafaxine in healthy volunteers using the pupillary light reflex as a test system. We used desipramine, a tricyclic antidepressant with potent noradrenaline re-uptake inhibiting properties but little action on serotonin re-uptake (Richelson 1994), and paroxetine, a selective serotonin re-uptake inhibitor with little effect on noradrenaline re-uptake (Richelson and Nelson 1984), as controls. Some of these results have been communicated to the British Association for Psychopharmacology (Bitsios et al. 1997).

Materials and methods

Subjects

Fifteen healthy male volunteers aged 20–28 years (mean ± SEM 22.00 ± 1.0) and weighing 57–105 kg (mean ± SEM 76.0 ±5.8) participated in the study. Subjects were all medication-free and were requested to stop smoking and to avoid drinking alcohol, coffee and other caffeine-containing beverages for at least 12 h before the experimental session. All of them were using tobacco and caffeine occasionally and all were occasional social alcohol consumers. They were all tested in the morning hours (9:00 a.m.–14:00 p.m.). The study protocol was approved by the University of Nottingham Medical School Ethics Committee. All volunteers gave their written consent following a verbal explanation of the study and after reading a detailed information sheet.

Drugs

Venlafaxine 75 mg and 150 mg, paroxetine 20 mg, desipramine 100 mg, and placebo were administered orally in matching capsules. In each session the subjects ingested one capsule on two occasions: one of the capsules contained the active drug and the other the placebo, except in the placebo session when both capsules contained placebo. The first capsule, containing desipramine, paroxetine or placebo was ingested 180 min and the second capsule, containing venlafaxine 75 mg, venlafaxine 150 mg or placebo, 100 min prior to testing.

Design

Subjects participated in five weekly sessions. Subjects were allocated to drugs and sessions according to a double-blind, balanced, cross-over design. A double-dummy procedure (see above, Drugs) was adopted in order to account for the different absorption kinetics of the active drugs. It has been reported that the peak concentration after a single oral dose of desipramine (Sallee and Pollock 1990) and paroxetine (Kaye et al. 1990) is attained approximately 3 h after ingestion, whereas the peak concentration is obtained approximately 2 h after the ingestion of venlafaxine (Kamerus et al. 1992).

Apparatus, stimuli and procedures

An infrared binocular television pupillometer (TVP 1015B Applied Science Laboratories, Waltham, Mass., USA) was used for the

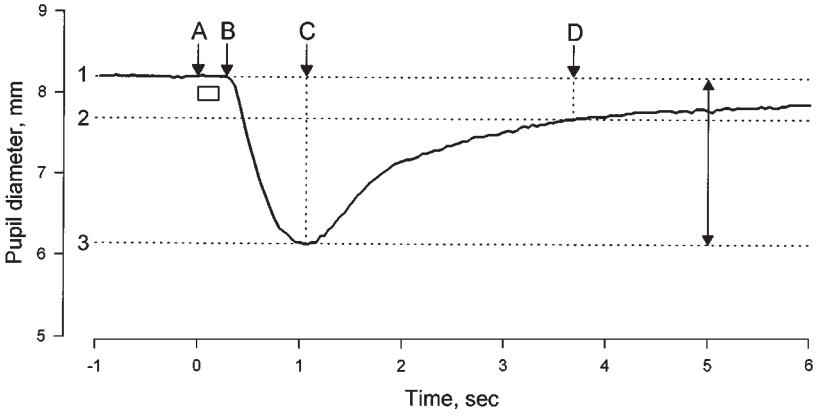

Fig. 1 Example of a light reflex response. *Ordinate:* pupil diameter (mm), *abscissa:* running time (s). *Horizontal bar*: light stimulus; *1* initial pupil diameter; *2* 75% recovery; *3* pupil diameter at maximal constriction; *A* onset of light stimulus; *B* onset of response; *C* time of maximal constriction; *D* time at which 75% recovery is attained; *1–3* amplitude; *AB* latency; *CD* 75% recovery time

recording of resting pupil diameter and the pupillary light reflex in darkness, in previously dark-adapted eyes. The experimental session started with three 45-s recordings of resting pupil diameter, the average of which served as the pre-treatment baseline resting pupil diameter. Three hours after ingestion of the first capsule (100 min after ingestion of the second capsule), recordings of resting pupil diameter were repeated and then the pupillary light reflex response was studied. The stimuli were six light flashes (green, 565 nm peak wavelength) of 200 ms duration, and of incremental illuminance (measured in the plane of the cornea): 3.0×10^{-3}, 8.5×10^{-3}, 2.5×10^{-2}, 7.0×10^{-2}, 0.18, 0.43 mW cm^{-1}. The light flashes were delivered at 25 s intervals, via a light emitting diode positioned 1 cm from the cornea of the subject's right eye. The recordings took place in a dark, sound-attenuated room and the subjects fixed their gaze on a dim red spot of light positioned approximately 2.5 m in front of them. Stimulus presentation was controlled by a microcomputer, and pupillary measures were digitized and stored on a floppy disk for off-line analysis. The parameters studied were: latency (i.e. time elapsing from the onset of the stimulus to the onset of the response, s), amplitude of light reflex response (i.e. the difference between the initial and the minimal diameters of a pupillary response to a light flash, mm) and 75% recovery time (i.e. time taken from the peak of the response to obtain 75% recovery, s) (see Fig. 1). Each light reflex response was visually inspected. If an eye-blink occurred either during the presentation of the stimulus, reducing the amount of light reaching the retina, or at the peak of pupillary constriction, rendering the amplitude immeasureable, the response in question was not included in the analysis.

Data analysis

Data obtained from the left pupil were analyzed. The post/pre-treatment difference was calculated for resting pupil diameter in darkness for each subject and for the group of 15 subjects. One-way analysis of variance with repeated measures with treatment as the within-subject factor followed by post hoc tests (least significant difference test) were used to compare the effects of treatment on resting pupil diameter in darkness. Separate two-way analyses of variance with repeated measures, with treatment (five levels) and light intensity (six levels) as the within-subject factors, were used to analyze each light reflex measure (i.e. latency, amplitude, 75% recovery time). In the case of a significant effect of treatment, multiple comparisons between placebo and the four active treatments were undertaken using Dunnett's test ($df = 56$, $k = 5$, criterion $P < 0.05$). The relationship between response amplitude and recovery time was analyzed using the product moment correlation coefficient, and best fit linear functions were derived with the method of least squares. Unpaired t-test was used to compare the slope values for each active drug and placebo.

Results

The effects of the treatments on resting pupil diameter in darkness are shown in Fig. 2 and Table 1. It can be seen that all treatments caused an increase in resting pupil diameter. One-way analysis of variance showed that the effect of treatment was significant ($F = 4.2$; df: 4,56; $P < 0.005$). Post hoc comparisons with the least significant difference test showed that only the increases caused by 75 and 150 mg of venlafaxine were significant.

The latency, amplitude and 75% recovery time of the light reflex response (group means) are displayed in Fig. 3. It can be seen that latency was prolonged with venlafaxine 75 mg and more so with venlafaxine 150 mg. Analysis of variance of the latency data revealed significant main effects of treatment ($F = 5.19$; df: 4,56, $P < 0.001$) and light intensity ($F = 83.5$; df: 5,70; $P < 0.001$) but no significant interaction ($F < 1$). Comparisons between placebo and the four active treatments using Dunnett's test showed that only the effect of venlafaxine 150 mg was significant ($t = 3.70$).

It can be seen that amplitude was smaller with venlafaxine 75 mg than under the placebo condition, and more so with venlafaxine 150 mg. Analysis of variance of the amplitude data revealed significant main effects of treatment ($F = 21.8$; df: 4,56; $P < 0.001$) and light intensity ($F = 339.6$; df: 5,70; $P < 0.001$) but no significant interaction ($F = 1$; df: 20,280; $P > 0.1$). Comparisons between placebo and the four active treatments using Dunnett's test showed that the effects of venlafaxine 75 and 150 mg were significant ($t = 5.46$ and 7.63, respectively).

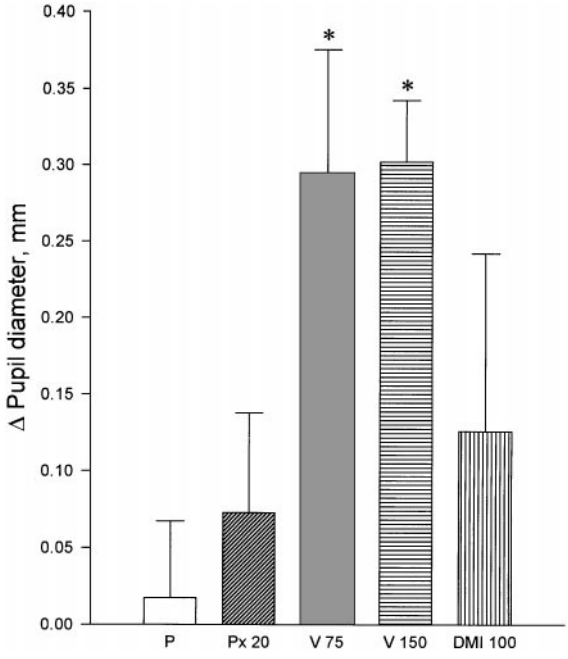

Fig. 2 Change in resting pupil diameter in darkness (mm) from pre-treatment baseline, in the presence of the five treatments. *P:* placebo, *Px 20:* paroxetine 20 mg, *V75:* venlafaxine 75 mg, *V150:* venlafaxine 150 mg, *DMI100:* desipramine 100 mg. The heights of the columns correspond to the means obtained in the group of 15 subjects; *vertical bars* are SEM. *Asterisks* denote statistical significance; $*P < 0.001$

Table 1 Effects of treatments on pupil diameter (mm): differences from values obtained after placebo

Treatment	Comparison with placebo: mean difference (95% CI)
Desipramine	0.109 (−0.182, 0.40)
Paroxetine	0.054 (−0.070, 0.18)
Venlafaxine 75 mg	0.275 (0.083, 0.467)
Venlafaxine 150 mg	0.283 (0.174, 0.391)

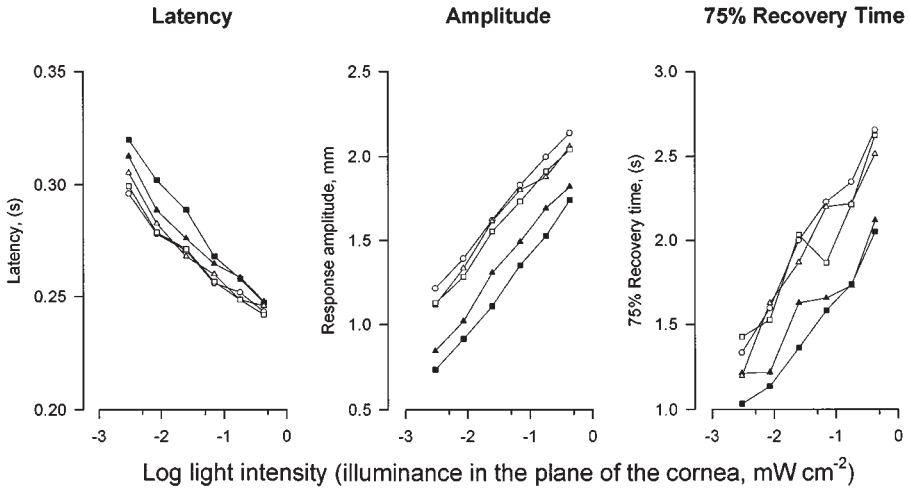

Fig. 3 Parameters of the light reflex response obtained at six graded illuminance levels, measured in the plane of the cornea, in the presence of the five treatments. *Open circles:* placebo; *open triangles:* paroxetine; *open squares:* desipramine; *closed triangles:* venlafaxine 75 mg; *closed squares:* venlafaxine 150 mg

It can be seen that recovery time was shorter with both venlafaxine treatments. Analysis of variance of the recovery time data revealed significant main effects of treatment ($F = 4.84$; *df*: 4,56; $P < 0.002$) and light intensity ($F = 24.9$; *df*: 5,70; $P < 0.001$) but no significant interaction ($F < 1$). Comparisons between placebo and the four active treatments using Dunnett's test showed that the effects of venlafaxine 75 and 150 mg were significant ($t = 2.79$ and 3.45, respectively).

The possibility that the changes in light reflex recovery time were secondary to changes in amplitude was also explored. The relationship between reflex response amplitude and 75% recovery time, at each light intensity value studied, is shown in Fig. 4; the results of the linear regression analysis are displayed in Table 2. It can be seen from Fig. 4 that the regression lines obtained after placebo and paroxetine did not deviate from each other, whereas the regression lines obtained after desipramine and venlafaxine deviated from that obtained after placebo. Statistical comparison of the slopes of the regression lines obtained in the presence of the antidepressants and placebo showed that the slopes obtained after the two doses of venlafaxine significantly differed from that obtained after placebo (unpaired *t*-test: venlafaxine 75 mg versus placebo $t = 3.09$, *df*: 10, $P < 0.02$; venlafaxine 150 mg versus placebo $t = 3.71$, *df*: 10, $P < 0.01$). There were no statistically significant differences between the slopes obtained after paroxetine and placebo ($t = 0.34$, *df*: 10, $P > 0.1$) or desipramine and placebo ($t = 0.86$, *df*: 10, $P > 0.1$).

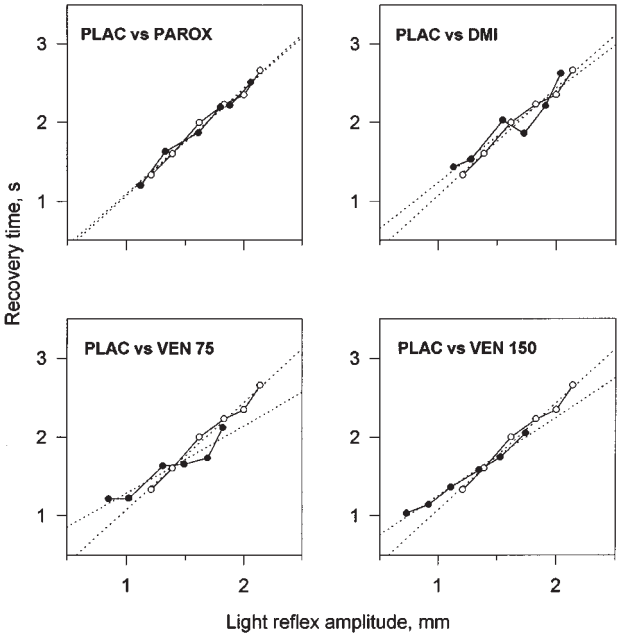

Fig. 4 Relationship between the amplitude and 75% recovery time of the light reflex responses evoked by the range of light stimulus intensities shown in Fig. 3. *Open circles:* placebo; *closed circles:* active treatment; the *dotted lines* were fitted with linear regression analysis; for statistical analysis see text and Table 1

Discussion

Resting pupil diameter reflects the balance between the opposing sympathetic and parasympathetic innervations of the iris, sympathetic activation increasing and parasympathetic activation decreasing resting pupil size (Loewenfeld 1993). Tricyclic antidepressants have variable effects on resting pupil diameter, depending on the balance between their ability to block noradrenaline uptake/post-junctional muscarinic cholinoceptors, effects which would tend to increase pupil diameter, and their ability to block post-junctional α_1-adrenoceptors, an effect which would tend to decrease pupil diameter (Szabadi and Bradshaw 1986). The tricyclic antidepressant used in the present experiment, desipramine, is a potent inhibitor of noradrenaline reuptake and has relatively low affinities for muscarinic cholinoceptors and α_1-adrenoceptors (Richelson 1994). The predicted effect of desipramine on resting

Table 2 Results of linear regression analysis (least squares, product moment correlation) of data displayed in Fig. 4

	Slope ± SE estimate	Intercept ± SE estimate	Correlation coefficient
Placebo	1.365 ± 0.081	−0.290 ± 0.139	0.99
Paroxetine 20 mg	1.326 ± 0.083	−0.228 ± 0.138	0.99
Desipramine 100 mg	1.168 ± 0.213	0.069 ± 0.349	0.94
Venlafaxine 75 mg	0.860 ± 0.142*	0.421 ± 0.200	0.95
Venlafaxine 150 mg	1.00 ± 0.056*	0.252 ± 0.710	0.99

*Slope significantly different from placebo condition, $P < 0.02$ (see text)

pupil size would be mydriasis, reflecting mainly noradrenaline reuptake. In the present experiment, a single dose (100 mg) of desipramine failed to have a significant effect on pupil diameter, consistent with a previous observation in our laboratory (Theofilopoulos et al. 1995). It should be noted, however, that in some other studies a mydriatic effect of desipramine could be observed (Szabadi et al. 1980, 1998; Shur and Checkley 1982; Kerr and Szabadi 1985). It seems, therefore, that the mydriasis observed after the administration of desipramine is not a consistent finding. The basis for the inconsistency may lie in the fact that desipramine also blocks α_1-adrenoceptors, and the relationship between the mydriasis resulting from noradrenaline reuptake blockade and the miosis from α_1-adrenoceptor blockade may differ between different experiments.

Both single doses (75 and 150 mg) of venlafaxine caused an increase in dark-adapted resting pupil diameter. This observation is in agreement with an earlier report demonstrating the mydriatic effect of smaller single doses (12.5, 25 and 50 mg) of venlafaxine (Saletu et al. 1992). As venlafaxine has practically no affinity for muscarinic cholinoceptors (Preskorn 1994), but has the ability to block noradrenaline uptake (Muth et al. 1986; Richelson 1994), the most likely explanation for venlafaxine-evoked mydriasis is that it reflects the blockade of noradrenaline uptake into sympathetic nerve terminals in the iris, which in turn results in the potentiation of the influence of the sympathetic input to the pupil dilator muscle.

As venlafaxine blocks not only noradrenaline but also 5-hydroxytryptamine (re)uptake in the brain (Muth et al. 1986; Richelson 1994), it should be considered whether the mydriasis evoked by venlafaxine might have been, at least partly, mediated by a serotonergic mechanism. Indeed, there is evidence that such mechanisms may be involved in pupillary control. Thus it has been reported that both 5-HT_2 receptor antagonists (Millson et al. 1991, 1992) and $5HT_{1A}$ receptor agonists (Fanciullacci et al. 1995; Phillips et al. 1998) cause miosis. On the other hand, fenfluramine, a drug known to release 5HT from pre-synaptic terminals, increases pupil diameter (Kramer et al. 1973). However, therapeutically relevant single doses of the SSRIs fluvoxamine (50–100 mg: Wilson et al. 1983; Flett et al. 1992) and paroxetine (20 mg: present study), when compared to placebo, have no significant effect on pupil diameter. Therefore, it is unlikely that the mydriasis caused by venlafaxine was due to the blockade of 5HT (re)uptake. Furthermore, the selective noradrenaline reuptake inhibitor (NARI) reboxetine, which has virtually no affinity for 5HT uptake (Brunello and Racagni 1998), also causes mydriasis (Szabadi et al. 1998), supporting the hypothesis that the mydriatic effect of venlafaxine is due to the blockade of noradrenaline uptake.

It is well known that there is a correlation between the level of physiological arousal and pupil diameter, sedation being accompanied by miosis and activation by mydriasis (Loewenfeld 1993). In this respect, it is of interest that venlafaxine has been reported to have a desipramine-like activating effect on the EEG, especially at a dosage of 50 mg and above (Saletu et al. 1992; Patat et al. 1998). Furthermore, venlafaxine shows some alerting effect in both psychophysiological tests (e.g. critical flicker fusion frequency) and subjective ratings of level of alertness (Saletu et al. 1998). It is likely that the alerting effect of venlafaxine is due to central noradrenergic activation (Foote and Aston-Jones 1995) resulting from the blockade of noradrenaline uptake in the brain. Interestingly, central noradrenergic activation may also contribute to the mydriasis by enhancing the tonic noradrenergic inhibition of the Edinger-Westphal nucleus (see below).

Venlafaxine also had distinctive effects on the kinetic parameters of the light reflex response, prolonging the latency, reducing the amplitude and shortening the recovery time of the response. The shortening of the recovery time could have been secondary to the reduction in the amplitude of the reflex response, since it is well documented that smaller light reflex responses take a shorter time to recover (Smith 1988; Theofilopoulos et al. 1995). However, it is unlikely that the reduction in amplitude can fully explain the shortening of the recovery time in the present experiment, since the statistical analysis of the relationship between amplitude and recovery time showed that the two doses of venlafaxine shortened the recovery time over and above that predicted on the basis of a reduction in amplitude alone. Thus, the shortening of the recovery time seems to be consistent with a genuine alteration in the autonomic components of the light reflex response. In fact, the effect on the recovery time is consistent with the blockade of noradrenaline uptake in the iris, leading to sympathetic potentiation. There is evidence that the recovery time is modulated by sympathetic activity: variables which increase sympathetic activity [e.g. heat

stressor (Leung et al. 1992; Mortlock et al. 1996)] shorten the recovery time, whereas variables which decrease the sympathetic influence on the iris [e.g. the centrally acting sympatholytic drug clonidine (Morley et al. 1991) and the α_1-adrenoceptor antagonist prazosin (Mortlock et al. 1996)] prolong the recovery time. Again, this effect was not shared by the SSRI paroxetine, consistent with previous findings with another SSRI, fluvoxamine (Flett et al. 1992), indicating that central 5HT reuptake blockade by venlafaxine is unlikely to be involved in the shortening of the recovery time. Furthermore, the selective noradrenaline reuptake inhibitor reboxetine, which has no effect on 5HT uptake, causes a similar shortening of the recovery time of the light reflex response (Theofilopoulos et al. 1995).

The prolongation of the latency and reduction of amplitude of the light reflex response, observed after the administration of venlafaxine, are surprising findings, since these effects are generally attributed to parasympathetic inhibition (Smith 1988), and venlafaxine has virtually no affinity for muscarinic cholinoceptors (Preskorn 1994). An alternative explanation may be that this "pseudo-anticholinergic" effect of venlafaxine is due to noradrenergic potentiation in the brain, again resulting from noradrenaline uptake blockade. There is evidence that the pre-ganglionic parasympathetic cholinergic neurones in the Edinger-Westphal nucleus of the mid-brain are under tonic inhibitory noradrenergic control from the locus coeruleus (for review, see Szabadi and Bradshaw 1996): the blockade of noradrenaline uptake at the inhibitory noradrenergic synapses in the Edinger-Westphal nucleus would "switch off" the parasympathetic neurones, resulting in a pseudo-anticholinergic effect in the periphery. Indeed, the opposite effect, i.e. disinhibition resulting in the enhancement of the light reflex response, can be observed when the inhibitory input from the locus coeruleus is "switched off" by the α_2-adrenoceptor agonist clonidine (Szabadi and Bradshaw 1996). It is of interest that the selective noradrenaline reuptake inhibitor reboxetine, which like venlafaxine has little affinity for muscarinic cholinoceptors (Brunello and Racagni 1998), has a similar inhibitory ("pseudo-anticholinergic") effect on the light reflex response (Theofilopoulos et al. 1995).

In conclusion, the pupillary effects of single doses of venlafaxine are consistent with the ability of the drug to block noradrenaline reuptake and thereby potentiate the pharmacological effects of endogenously released noradrenaline. The blockade of noradrenaline reuptake at the noradrenergic sympathetic effector junction in the iris could explain the mydriasis and the shortening of the recovery time of the light reflex response, whereas the blockade of noradrenaline reuptake at the inhibitory noradrenergic synapses on Edinger-Westphal neurones may be responsible for the pseudo-anticholinergic pupillary effects of the drug (i.e. prolongation of the latency and reduction of the amplitude of the light reflex response, and, to some extent, the mydriasis). It is of interest that venlafaxine, like the selective noradrenaline reuptake inhibitor reboxetine (Szabadi et al. 1998), displays a similar pseudo-anticholinergic effect on salivary gland activity (Abdelmawla et al. 1997b), probably resulting from the potentiation of the central noradrenergic inhibition of the salivary nuclei in the brain stem.

In the present study, both single doses (75 and 150 mg) of venlafaxine exerted effects consistent with the blockade of noradrenaline uptake both in the periphery and the central nervous system. It is of interest that in another report (Abdelmawla et al. 1997a), in which the effects of the same doses of venlafaxine on noradrenergic responses of the dorsal hand vein were studied, only the higher dose potentiated the response to noradrenaline. These observations indicate a difference between the effects of the drug on responses evoked by endogenously released and exogenously applied noradrenaline: for potentiation of responses to exogenously applied noradrenaline higher dosages of venlafaxine are required than for the potentiation of the effects of endogenously released noradrenaline. Therefore, it is likely that patients treated even with lower dosages of venlafaxine may experience some enhancement of the pharmacodynamic effects of endogenous noradrenaline.

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