The Effect of Desipramine upon Central Adrenergic Function in Depressed Patients

I. B. GLASS, S. A. CHECKLEY, E. SHUR and S. DAWLING

Summary: Eleven drugfree patients meeting Research Diagnostic Criteria for Major Depressive Disorder have been treated with desipramine and given a clonidine infusion after 0, 1 and 3 weeks of treatment. The sedative and hypotensive effects of clonidine were significantly inhibited after three weeks of treatment with desipramine: a similar interaction was seen after one week of treatment although this just failed to reach statistical significance. The growth hormone (GH) response to clonidine was initially impaired, but increased significantly after one week of treatment. A significant reduction in the GH response occurred during the second and third weeks of treatment with desipramine. This last finding is interpreted as evidence of adaptive change of $\alpha_2$ adrenoceptors: the other changes can be explained by the known ability of desipramine to block the re-uptake of noradrenaline.

The tricyclic antidepressants have many pharmacological properties including the ability to block the re-uptake of noradrenaline, of 5-hydroxy-tryptamine and in some cases of dopamine, and to block the receptors at which noradrenaline, 5-hydroxytryptamine, dopamine, histamine and acetylcholine act (for reviews see Sulser, 1978; Sugrue, 1981a). In addition to these acute effects chronic treatment with tricyclic drugs alters the number, function and circadian rhythm of $\alpha$ and $\beta$ adrenoceptors and of dopamine and 5-hydroxytryptamine receptors (Creese and Sibley, 1980; Charney et al., 1981a; Sugrue, 1981b). However the clinical relevance of these animal findings is uncertain as it is unknown which of these effects occur in clinical practice and which are necessary for the antidepressant action of tricyclic drugs.

Animal studies of the effects of antidepressant drugs upon noradrenaline have used desipramine as a relatively selective inhibitor of the re-uptake of noradrenaline (Maitre et al., 1980). A single dose of desipramine causes a potent inhibition of noradrenaline re-uptake together with a weaker blockade of post-synaptic $\alpha_1$ adrenoceptors (U'Prichard et al., 1978). Three weeks of desipramine additionally leads to a reduction in the number and function of $\beta$ adrenoceptors (for reviews see Creese and Sibley, 1980; Charney et al., 1981a; Sugrue, 1981a and b) and of $\alpha_2$ adrenoceptors (Crews and Smith, 1978 and 1980; Svensson and Usdin, 1978; Tang et al., 1978 and 1979; McMillen et al., 1980; Sypraki and Fibiger, 1980; Sugrue, 1981c). These slowly developing adaptive changes in $\alpha$ and $\beta$ adrenoceptors may be relevant to the mechanisms of action of antidepressant drugs, particularly as their time course follows that of the antidepressant effect of these drugs.

To investigate whether or not similar changes in $\alpha_2$ adrenoceptors occur in patients treated with desipramine, we have given such patients infusions of clonidine and have measured the effects of clonidine upon growth hormone (GH), blood pressure and sedation. As discussed previously (Checkley et al., 1981a) it is likely that all of these effects of clonidine depend upon the stimulation of $\alpha_2$ adrenoceptors. Consequently if treatment with desipramine alters $\alpha_2$ adrenoceptors then it should alter the effects of clonidine upon GH, blood pressure and sedation.

We have previously shown that three weeks of treatment with desipramine inhibits the hypotensive and sedative effects of clonidine (Checkley et al., 1981b). Recently others have replicated the inhibition by chronic desipramine treatment of the hypotensive effect of clonidine (Charney et al., 1981b) and it has long been known that acute treatment with tricyclic antidepressants inhibits the hypotensive effect of chronic clonidine treatment (Briant et al., 1973). Charney also showed that chronic treatment with desipramine inhibited the ability of clonidine to suppress plasma concentrations of 3-methoxy-4-hydroxy phenylethylene glycol (MHPG) (Charney et al., 1981b). All these findings suggest that desipramine alters the responses to the stimulation of $\alpha_2$ adrenoceptors in man. To investigate these phenomena further, we have now studied the interactions with clonidine after one as well as after three weeks of treatment with desipramine. As well as replicating our earlier findings we now present neuroendocrine
findings which may represent the first evidence of central neuroceptor adaptation in patients being treated with an antidepressant.

Methods
Depressed patients were selected who met Research Diagnostic Criteria (Spitzer et al, 1977) for major depressive illness and who had been free of psychotropic drugs other than benzodiazepines for at least three weeks. Patients were excluded if their alcohol consumption exceeded two litres of beer or its equivalent per day, if they had any endocrine disorder, if they had severe cardiorespiratory disorder or a resting systolic blood pressure below 110 mHg. Patients detained on a section of the Mental Health Act were not permitted to participate. Prior to the clonidine tests, physical examination, electrocardiography, chest X-ray, routine haematological and biochemical investigations were performed.

Before treatment patients were assessed using the Schedule for Affective Disorders and Schizophrenia (Endicot and Spitzer, 1978), the Hamilton Rating Scale for use in Depression (Hamilton, 1967) and the Carney, Roth, Garside (1965) questionnaire. Patients were then treated with desipramine: the initial dose of 2 mg/kg body weight was adjusted rapidly over the first week of treatment according to side effects. Clonidine tests were performed as described previously (Checkley et al, 1981a) but using a smaller dose of clonidine.

Tests were performed after 0, 1 and 3 weeks of treatment with desipramine. Patients were fasted overnight and at 9.30 a.m. a catheter was inserted into a forearm vein. For 30 minutes or more no observations were made. Baseline observations were then made for 30 minutes. The clonidine (1.3 μg/kg body weight) was diluted in 10 ml normal saline and injected slowly over 10 minutes. Observations were continued for 90 minutes after starting the injection. Throughout the procedure pulse and blood pressure were recorded every 5 minutes, sedation was rated on a 5-point scale every 5 minutes and blood samples for GH estimation were taken every 15 minutes.

Plasma desipramine concentrations after 1 and 3 weeks of treatment were estimated using gas liquid chromatography with nitrogen detection (Braithwaite, 1979). GH estimations were made using a double antibody radioimmunoassay; any set of GH data was excluded from analysis if the baseline GH concentration exceeded 3 ng/ml. The response of each variable was plotted graphically against time and the area under the curve following injection of the drug was calculated. Paired comparisons were made using Wilcoxon's signed Rank Test.

Results
The 11 patients included 4 females. The mean age of the group was 39.7 years (range 23–62); 9 met clinical and research diagnostic criteria (Spitzer et al, 1977) for endogenous depression and 6 had diagnostic scores in the endogenous range on the Carney, Roth, Garside (1965) questionnaire. Their mean Hamilton rating score was 21 (range 13–33) before treatment, 13 (range 0–31) after one week of treatment and 10 (range 0–24) after three weeks of treatment with desipramine. The mean plasma desipramine concentration was 88.5 μg/l (range 31–265) after one week and 132 μg/l (range 28–560) after three weeks of treatment. The following interactions were unrelated to plasma desipramine concentrations.

Prior to treatment with desipramine, the growth hormone response to clonidine was impaired (Fig 1) as has been described previously (Matussek et al, 1980; Checkley et al, 1981a). After one week's treatment with desipramine growth hormone release was significantly enhanced (P <.025). Between one and three weeks' treatment with desipramine, the growth hormone response became attenuated (P <0.025), and after three weeks of treatment the GH response to clonidine was no longer significantly greater than before treatment. The response seen after one week of treatment was similar to that of normal subjects (Checkley et al, 1981a).

The hypotensive effects of clonidine are shown in Figs 2 and 3. In untreated depressed patients clonidine exerted its usual hypotensive effect and this effect was inhibited after one and three weeks of treatment with desipramine. After one week of treatment there was an inhibition of the fall in systolic blood pressure which just failed to reach statistical significance (P <.054): after three weeks of treatment the fall in both systolic (P <.042) and diastolic (P <.05) blood pressure was inhibited.

Observer ratings of sedation are shown in Fig 4. The sedative effective of clonidine was inhibited after three weeks' treatment with desipramine (P <.01).

Discussion
This report confirms our previous finding that three weeks of treatment with desipramine inhibits the sedative and hypotensive effects of clonidine and we now report similar interactions after only one week of treatment. The fact that no further change occurs during the second and third weeks of treatment suggests that these effects are due to an acute drug effect and not to a chronic adaptive change. Similar interactions between clonidine and desipramine have been demonstrated in brain slices from which the stimulus-evoked release of labelled noradrenaline can
EFFECT OF DESIPRAMINE UPON CENTRAL ADRENERGIC FUNCTION

Fig 1.—Median plasma GH concentrations in depressed patients after 0, 1 and 3 weeks of treatment with desipramine. On each occasion patients received an intravenous infusion of clonidine (1.3 μg/kgm body weight) over 10 minutes starting at time 0. (The two figures include data from different pairs of 8 observations, as a pair of data from a patient are only included if the baseline GH concentration is less than 3 ng/ml on both occasions).

Fig 2.—Mean systolic and diastolic blood pressure (±SEM) following a clonidine infusion in 11 depressed patients before and after one week of treatment with desipramine.

Fig 3.—Mean systolic and diastolic blood pressure (±SEM) following a clonidine infusion in 11 depressed patients before and after three weeks of treatment with desipramine.

be measured (Pelayo et al, 1980). In this preparation clonidine reduces the release of noradrenaline, presumably by stimulating pre-synaptic α₂ adrenoceptors whose function is to inhibit noradrenaline release. Under the same conditions desipramine increases the release of noradrenaline from brain slices, presumably as a result of uptake blockade. It follows that desipramine should inhibit the effect of clonidine upon noradrenaline release, and this has been demonstrated (Pelayo et al, 1980). A similar interaction between clonidine and desipramine would explain how in our patients desipramine inhibits the sedative and hypotensive effects of clonidine.

The present report contains the new and paradoxical finding that whereas the sedative and hypotensive effects of clonidine are inhibited by one week of treatment with desipramine the GH response is strikingly enhanced. This paradox may be due to the different effects of clonidine upon noradrenaline release in different brain regions. For whereas in the cerebral cortex clonidine reduces noradrenaline release, in the hypothalamus clonidine has the opposite effect (Rand et al, 1975; Medgett et al, 1978). The hypothalamus is the likely site of the adrenoceptors which mediate the GH response to clonidine and so the paradoxical ability of clonidine to increase nor-
adrenaline release in the hypothalamus may be linked with the GH response to clonidine. If this is so then treatment with desipramine should enhance the effect of clonidine upon the release of both noradrenaline in the hypothalamus and of GH from the pituitary.

All of the interactions which have been discussed so far may be attributed to the inhibition by desipramine of the re-uptake of noradrenaline and adaptive responses at \( \alpha_2 \) adrenoceptors need not be involved. However the concept of adaptive change at receptors is needed to explain our neuroendocrine findings. We have previously explained reduced GH responses to clonidine in untreated depressed patients by an \( \alpha \) adrenergic defect (Checkley, 1980; Checkley et al., 1981a). We have also explained the striking increase in the GH response to clonidine after one week of desipramine treatment (Fig 1) as an effect of inhibition of noradrenaline re-uptake. The third neuroendocrine finding is the attenuation of this increase in the GH response to clonidine during the second and third weeks of treatment with desipramine (Fig 1). The simplest explanation for this finding is a down-regulation of the \( \alpha_2 \) adrenoceptors at which clonidine acts to release GH. Interestingly, such an adaptive mechanism reduces but does not reverse the primary effect of desipramine upon the GH response to clonidine.

This discussion has been restricted to the simplest of the explanations for our findings. It would seem unlikely that clinical change has contributed to the results as the GH response to clonidine was not changed in depressed patients who recovered following treatment with ECT (Slade and Checkley, 1980). One strength of this neuroendocrine approach to psychopharmacology is the fact that very similar neuroendocrine testing is possible both in patients and in experimental animals as we have shown in our studies on the effects of ECT upon the GH response to clonidine in patients (Slade and Checkley, 1980) and baboons (McWilliam et al., 1981). The above explanations for our present findings are now amenable to test in similar animal experiments.

Acknowledgements

This study was generously supported by the Wellcome Trust and the Medical Research Council and was conducted with guidance and support from Dr J. L. Crammer. We thank Mr D. Yeoman for his careful execution of the hormone assays, and the Pharmacy Staff at The Maudsley Hospital for the supply of test drugs.

References


EFFECT OF DESIPRAMINE UPON CENTRAL ADRENERGIC FUNCTION


Ilana B. Glass, M.A., M.B., B.Ch., M.R.C.Psych., Research Worker, Institute of Psychiatry, De Crespigny Park, London, SE5 8AF

Stuart A. Checkley, B.M., M.R.C.P.(U.K.), M.R.C.Psych., Consultant Psychiatrist, Maudsley Hospital, London, SE5 6AZ

Eric Shur, M.B., B.Ch., M.R.C.Psych., Lecturer in Psychiatry, Institute of Psychiatry

Sheila Dawling, B.Sc., Poisons Unit, Guy's Hospital, London, SE1

(Received 22 February 1982)
The effect of desipramine upon central adrenergic function in depressed patients.
I B Glass, S A Checkley, E Shur and S Dawling
Access the most recent version at DOI: 10.1192/bjp.141.4.372

References
This article cites 0 articles, 0 of which you can access for free at:
http://bjp.rcpsych.org/content/141/4/372#BIBL

Reprints/permissions
To obtain reprints or permission to reproduce material from this paper, please write to permissions/rcpsych.ac.uk

You can respond to this article at
/letters/submit/bjprcpsych;141/4/372

Downloaded from
http://bjp.rcpsych.org/ on June 25, 2017
Published by The Royal College of Psychiatrists