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THE RESPONSIVENESS OF SWEAT GLANDS TO CARBACHOL IN ANXIETY NEUROSIS

Patients suffering from anxiety neurosis frequently complain of increased sweating (Lader, 1975). Under laboratory conditions, evidence for increased sweat gland activity in anxious patients, as compared to that seen in healthy subjects, has been obtained both from skin conductance measurements (Lader & Wing, 1966), and from colourimetric estimation of sweat secretion (Silverman & Powell, 1944). It is not known, however, whether the pharmacological sensitivity of sweat glands is altered in anxiety neurosis. Sweat gland activity is largely controlled by cholinergic sympathetic nerves (Dobson & Sato, 1972), and local sweating can readily be evoked by intradermal injections of cholinomimetic agents (Dobson & Sato, 1972). The experiment reported here was an attempt to determine whether the increased sweating seen in anxious patients is accompanied by an altered sensitivity of sweat glands to intradermally injected carbachol.

Ten patients (three males and seven females; mean age 35.7 years) with a primary diagnosis of anxiety neurosis were studied. One patient was receiving diazepam 10 mg three times daily; the other nine patients had not received any drugs for at least 7 days before the experiment. The control group consisted of eleven healthy volunteers (six males and five females; mean age 27.5 years), none of whom had taken any drugs for at least 7 days before the experiment. Each subject completed the Leeds Anxiety Rating Scale (Snaith, Bridge & Hamilton, 1976) immediately before the experiment. The temperature in the experimental room was 21–22°C, and the relative

humidity was 47–60%. The subjects rested for at least 15 min before the experiment. Spontaneous ('baseline') and carbachol-evoked sweating on the volar surface of the forearm was measured using the plastic paint method of Clubley, Bye, Peck & Riddington (1978); an area of skin measuring 3.5 cm × 2.3 cm was used for each measurement. Initially the number of glands 'spontaneously' active was measured. Then the numbers of active glands were measured 30 s after the intradermal injection of six different doses of carbachol. Three injections were placed at equal distances on each forearm; the volume injected was always 0.05 ml, and the concentrations of carbachol chloride, dissolved in 0.154 M sodium chloride, were 5×10^{-6} M, 1×10^{-5} M, 5×10^{-5} M, 1×10^{-4} M, 5×10^{-4} M, and 1×10^{-3} M.

The median anxiety score for the patient group was 15.0, and that for the control group was 1.0 (Mann-Whitney U test: $P < 0.01$). The baseline number of active sweat glands was 17.7 (± 4.1) for the healthy volunteers and 108.9 (± 13.3) for the anxious patients (t -test: $P < 0.001$). The effects of intradermally injected carbachol on sweat gland activity in the two groups of subjects are shown in Figure 1. Best fit hyperbolic functions were fitted to the data by computer using an iterative procedure based on the method of Wilkinson (1961); this method provides estimates ($\pm$ s.e. estimate) of the maximum response to the agonist ($E_{\max}$), and the dose required to evoke the half-maximal response (ED_{50}). The values obtained for the two groups are shown in Table 1. The ED_{50} did not differ significantly between the two

Figure 1 The number of sweat glands activated by increasing concentrations of intradermally injected carbachol in eleven healthy volunteers (●—●) and ten anxious patients (○—○). Abscissa: concentration of drug solution (M) on a log scale; ordinate: number of active sweat glands. Points are mean obtained for each group; vertical bars indicate $\pm$ s.e. mean. Horizontal lines indicate number of sweat glands active under resting conditions, in the absence of carbachol. Curves are semilogarithmic transformations of best-fit hyperbolic functions fitted by the method of Wilkinson (1961): see text.

groups (t -test: $P > 0.1$). However the value of $E_{\max}$ was significantly greater for the anxious patients than for the healthy volunteers (t -test: $P < 0.05$). Values of the index of determination (p^2) were derived for the data obtained from each group; p^2 expresses the proportion of the data variance which can be accounted for by the fitted function (Lewis, 1960). The values of p^2 were 0.90 and 0.78 for the healthy volunteers and the patient group respectively.

The greater number of active sweat glands seen under resting conditions in the anxious patients than in the healthy volunteers is consistent with the evidence from skin conductance studies showing that

anxious patients have a higher baseline level of sweat secretion (Lader & Wing, 1966; Bond & James, 1974). The two groups of subjects did not differ significantly with respect to their ED_{50} values for carbachol; however the anxious patients had a significantly higher value of $E_{\max}$ than the healthy volunteers, indicating that a greater number of sweat glands were capable of being stimulated by carbachol in the anxious group. It is known that a considerable proportion of sweat glands are unresponsive to cholinergic agonists in normal subjects (Ogata & Ichihashi, 1935); possibly, some of these 'dormant' glands become capable of activation in anxiety states. It is of interest that another condition which increases baseline sweat gland activity, raised ambient temperature, also produces an enhanced sensitivity to cholinergic agonists (Benjamin, 1953); indeed, in a previous study in which the effects of intradermally injected carbachol were examined in healthy volunteers at a somewhat higher room temperature (23 – 24°C) than in the present study (21 – 22°C), we observed a greater baseline number of sweat glands (39.3 ± 2.3) and a higher value of $E_{\max}$ (215.6 ± 14.7) than those found with the control group in the present study (Szabadi, Gaszner & Bradshaw, 1980).

It is interesting to compare the change in pharmacological responsiveness of sweat glands in anxious patients seen here, and the previously reported changes in skin conductance in this group of patients (Lader & Wing, 1966). The increase in baseline skin conductance seen in anxious patients is accompanied by a *reduction* of the amplitude of emotionally evoked conductance changes, in accordance with the 'Law of Initial Values' (Lader & Wing, 1966). In contrast, the present results indicate that the increase in baseline sweat gland activity is accompanied by an *enhancement* of the maximum response to carbachol. Caution is needed, however, in comparing the present results with those of skin conductance studies. Skin conductance measurements are generally made on the volar surface of the hand, rather than on the forearm; it is

Table 1 Quantitative features of the dose-response curves shown in Figure 1

	$ED_{50} (\pm \text{s.e. estimate})$ concentration of carbachol ($\text{M} \times 10^{-5}$)	$E_{\max} (\pm \text{s.e. estimate})$ number of sweat glands activated
Healthy volunteers	$3.9 (\pm 1.9)^+$	$161.5 (\pm 18.4)^*$
Anxious patients	$6.2 (\pm 4.6)^+$	$266.6 (\pm 46.3)^*$

Significance of difference between values obtained from the two groups (t -test): + NS, * $P < 0.05$.

possible that changes in sweat gland responsiveness in anxiety states are different in these two skin regions.

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DECREASED CONJUGATED TYRAMINE OUTPUT IN DEPRESSION: THE EFFECT OF ORAL L-CYSTEINE

We have previously shown that orally administered anhydrous sodium sulphate (300 mg) has no significant effect on the excretion of conjugated tyramine (tyramine-*O*-sulphate), after an oral tyramine load (Bonham Carter, Sandler, Sepping & Bridges, 1978a). This was true both for a group of normal subjects and a group of patients suffering from severe depression who exhibited an apparent conjugation defect as previously reported (Sandler, Bonham Carter, Cuthbert & Pare, 1975; Bonham Carter, Sandler, Goodwin, Sepping & Bridges, 1978b), despite claims by Smith & Mitchell (1974) of an increase in tyramine-*O*-sulphate output after oral sodium sulphate administration. However, this finding was hardly surprising since the gut absorbs inorganic sulphate with difficulty (Fingl, 1965) and it does not rule out the possibility that the depressive subjects in whom we observe the apparent conjugation defect are suffering from chronic sulphate depletion associated with persistent administration of drugs which form sulphate conjugates (Levy & Matsuzawa, 1967; Bennett, Blackwell & Davies, 1975). The source or inorganic sulphate in the body is thought to be the sulphur containing amino acids such as cysteine (Sörbo, 1965) and an inadequate intake of cysteine

and other sulphur containing amino acids in the diet could be another possible explanation for the apparent conjugation defect observed in depressive illness. We set out to test this possibility by giving a dietary supplement of L-cysteine to normal subjects and depressed patients using a similar design to Levy & Matsuzawa (1967) and examining the effect on the conjugation of orally administered tyramine.

The experiment described was carried out on a group of six normal volunteers (three men and three women) and six severely depressed patients (all women) whose illnesses were resistant to all standard forms of treatment and who were about to undergo modified leucotomy (Knight, 1965; Göktepe, Young & Bridges, 1975; Bridges & Bartlett, 1977). The subjects were given 100 mg tyramine (125 mg tyramine hydrochloride) orally on one day and two successive 3 h urine collections were made as previously described (Sandler *et al.*, 1975). The specimens were acidified, diluted if necessary and an aliquot stored deep frozen until analysis (Bonham Carter *et al.*, 1978b). After a time interval of at least 48 h the tyramine loading was repeated with additional L-cysteine. L-Cysteine (1 g, as three capsules of 333 mg) was given orally every hour from