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The effect of β-adrenoceptor blockade on human sweating

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Summary

1. Changes in cutaneous water loss were followed by continuously monitoring total body weight loss.

2. Sweating was induced in normal subjects by raising the environmental temperature or by subjecting them to the emotional stress of mental arithmetic.

3. Propranolol in a dosage of 0·15 mg/kg body weight intravenously had no significant effect on either thermal or emotional sweating, whereas thermal sweating was completely blocked temporarily by administration of atropine 2·4 mg intravenously.

4. It is concluded that β-adrenoceptor blockade has no effect on physiological sweating in normal people.

Introduction

Excessive sweating is often a feature of thyrotoxicosis. Shanks, Hadden, Lowe, McDevitt & Montgomery (1969) reported that the β-adrenoceptor blocking agent, propranolol, controlled the cardiovascular symptoms of the disease and reduced other manifestations including the excessive sweating. Krikler (1966) also reported a reduction in sweating in thyrotoxic patients treated with propranolol. However, these reports were based on the clinical impressions of the observers and the subjective sensations of the patients ; no actual measurements were made.

Human sweating is known to be mediated by cholinergic sympathetic nerves and can be blocked by atropine (Chalmers & Keele, 1952). Propranolol, although primarily an adrenoceptor blocking agent, has been shown to reduce the effect of acetylcholine on uterine (Elwood, 1967), and vascular smooth muscle (Brick, Hutchison & Roddie, 1970), and other β-adrenoceptor blockers have been shown to decrease the effect of vagal stimulation on cardiac muscle (James & Nadeau, 1963 ; 1964). These actions may be due to a direct anti-acetylcholine effect of propranolol although this seems unlikely in view of the findings of Hedges & Turner (1971) that the pA_2 of propranolol was only about 4 suggesting that no significant anti-acetylcholine effect would ever be seen in therapeutic doses. Propranolol might also decrease the response of these tissues to acetylcholine by its local anaesthetic activity, since local anaesthetics have been shown to have a depressant action on many cholinergically innervated tissues (De Elio, 1948). Propranolol is in fact a potent local anaesthetic, having 2–3 times the local activity of procaine (Morales-Aguilera & Vaughan Williams, 1965).

The reported reduction in sweating in thyrotoxic patients treated with propranolol might be due to the action of the drug on the disease process itself. However, it could also be due to a direct anti-acetylcholine effect or to the local anaesthetic action of propranolol on the sweating mechanism. A direct action

due to its β-adrenoceptor blocking properties also seems possible in view of the finding that a small non-cholinergically mediated sweat response apparently dependent on β-adrenoceptor stimulation can be demonstrated during intravenous catecholamine infusions in normal subjects (Allen & Roddie, 1972). If propranolol has such a direct action on the sweating mechanism in thyrotoxic patients, it should be possible to demonstrate this in normal subjects. The purpose of the present experiments was to investigate the effects of propranolol on thermal and emotional sweating in normal subjects.

Methods

The subjects who were all young healthy medical students were at rest in a heat chamber in which the environmental temperature could be maintained constant at any desired temperature. The subjects were allowed to equilibrate to the temperature of the heat chamber for one hour before any measurements were made in experiments in an environmental temperature of greater than 29° C. Changes in sweating were estimated by continuously monitoring total body weight loss (Allen, Grimley & Roddie, 1971). Mouth, forehead and hand skin temperatures were monitored with thermocouples. Instantaneous heart rate was recorded continuously by a Devices instantaneous ratemeter (Type 2750) triggered by the QRS complex of lead II of the electrocardiogram.

Effects of propranolol on thermal sweating

Experiments were performed on each of 5 subjects at 2 environmental temperatures, 34° and 40° C. A cannula (Graham's Venflon) was inserted into an antecubital vein during the equilibration period. Total body weight loss was recorded for a one hour control period. (±)-Propranolol (Inderal, I.C.I. Ltd.) was then administered intravenously in a dose of 0·15 mg/kg body weight via the indwelling cannula over a 4 min period and recording was continued for a further hour.

Effects of atropine on thermal sweating

Experiments were performed on each of 4 subjects at environmental temperatures of 18°, 29° and 37° C. After one hour of control recordings, atropine (Evans Medical Ltd.) 2·4 mg was injected intravenously over 4 min and recording was continued for a further hour.

Effects of propranolol on emotional sweating

Emotional sweating was induced in each of 6 subjects on two occasions at an environmental temperature of 29° C. A cannula (Graham's Venflon) was inserted into an antecubital vein before the start of each experiment. On the first occasion, after 20 min control recordings, 3 of the subjects received an injection of propranolol (0·15 mg/kg body weight) intravenously over a period of 4 min, and the other 3 subjects received an injection of an equivalent volume of 0·9% w/v NaCl solution (saline). Recordings were continued for a further 20 min and then the subjects were given some moderately difficult verbal mental arithmetic problems to solve for 10 minutes. Recording was continued throughout this and for 15 min afterwards. On the second occasion, the protocol was exactly the same except that

those subjects who had received propranolol on the first occasion were given saline, and those who had previously received saline were given propranolol. The subjects themselves were unaware of the nature of the injection but the procedure was not double blind. Peak flow rates were measured before and after all experiments with a Wright Peak Flow Meter (Airmed Ltd.).

Weight loss was expressed in terms of $(g/m^2)/5$ min ; the formula of Du Bois & Du Bois (1916) was used to calculate surface area.

A different group of subjects was used for each of the three investigations.

Results

Effects of propranolol on thermal sweating

Figure 1 shows the record of a typical experiment in an environmental temperature of 40° C. Two traces of weight loss are shown. The upper one is a direct recording and fluctuations due to respiratory and other movements are apparent. The lower weight loss trace shows the integral every 30 s of the area under the direct weight loss slope. This eliminates movement artefact and all measurements were made from this trace. At this environmental temperature the subject was sweating freely, thus the rate of total body weight loss was rapid and the weight loss slopes have a correspondingly steep gradient. A 20 g weight was added to the system at intervals to compensate for the subject's weight loss. This produced

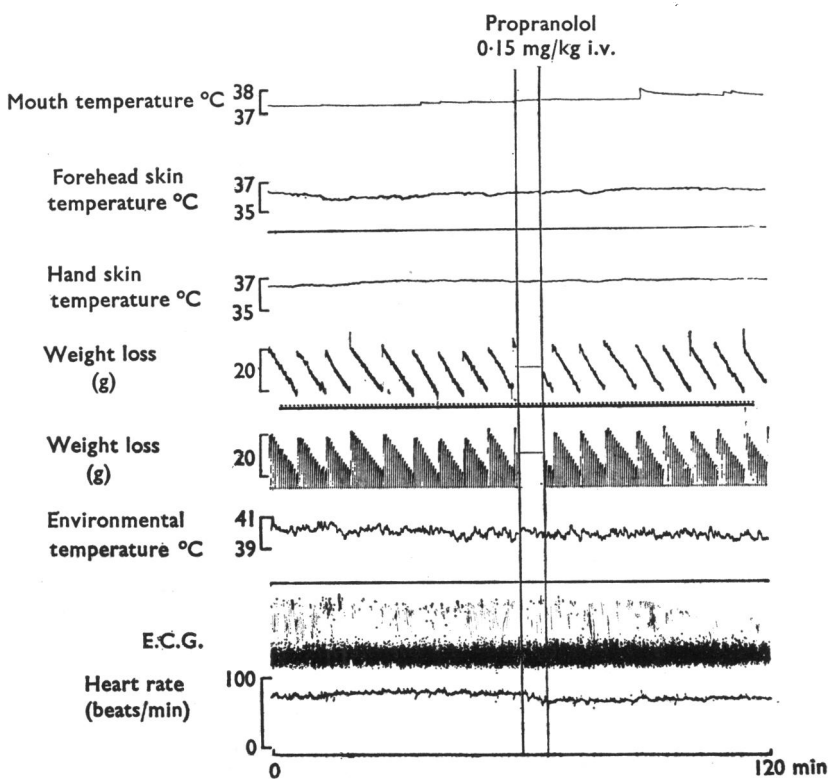

FIG. 1. The effects in one subject of the intravenous injection of propranolol in an environmental temperature of 40° C.

the sudden upward step in the weight loss traces apparent at approximately 6 min intervals during the 60 min control period. Injection of propranolol did not alter the rate of weight loss in this subject, the gradient of the weight loss slopes being unaltered following the injection. Mouth, forehead and hand skin temperatures were similarly unaltered, but heart rate fell following the administration of propranolol.

Figure 2 shows the mean results for the 5 subjects at 34° and 40° C. It can be seen that propranolol had no significant effect on thermally induced sweating at either temperature.

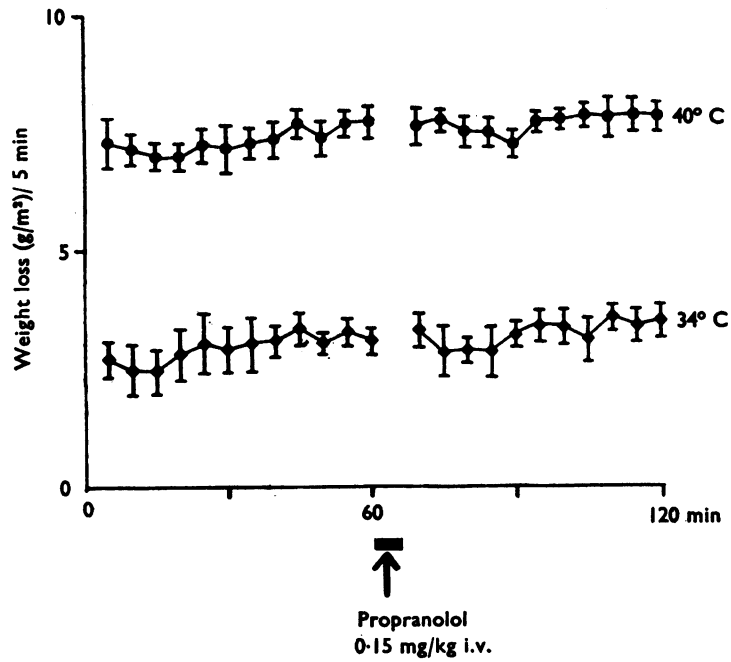

FIG. 2. The mean results of experiments on 5 subjects in which propranolol was injected intravenously at 34° and 40° C. Vertical bars show 1 S.E.M.

In all experiments there was a reduction in the resting heart rate after the administration of propranolol. At 34° C, the mean heart rate fell significantly ($P<0{\cdot}01$) from a control level of 66 beats/min (± 3) to 58 (± 2). At 40° C, it fell significantly ($P<0{\cdot}01$) from 77 (± 5) to 66 (± 4) beats /minute.

None of the body temperatures measured changed significantly during the course of the experiments.

Effects of atropine on thermal sweating

Figure 3 shows the record of a typical experiment in an environmental temperature of 37° C. Following the injection of atropine 2·4 mg the rate of weight loss immediately decreased, the weight loss slopes becoming much flatter, and heart rate increased. Over the next 30 min the rate of weight loss remained low, then it gradually began to increase so that by the end of the experiment the slopes were

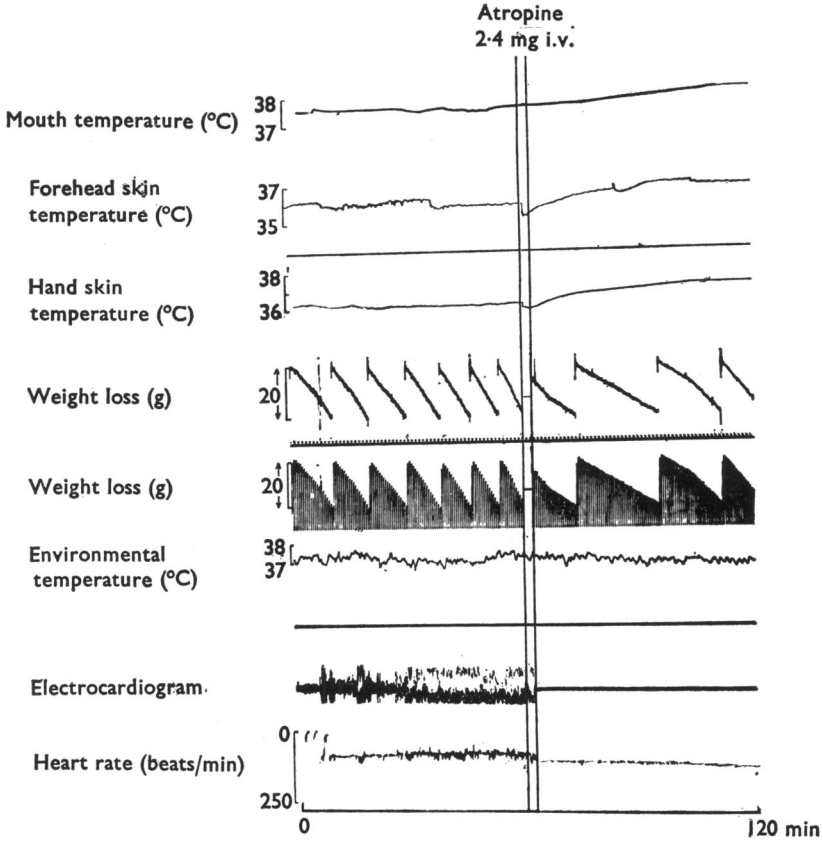

FIG. 3. The effects in one subject of the intravenous injection of atropine in an environmental temperature of 37° C.

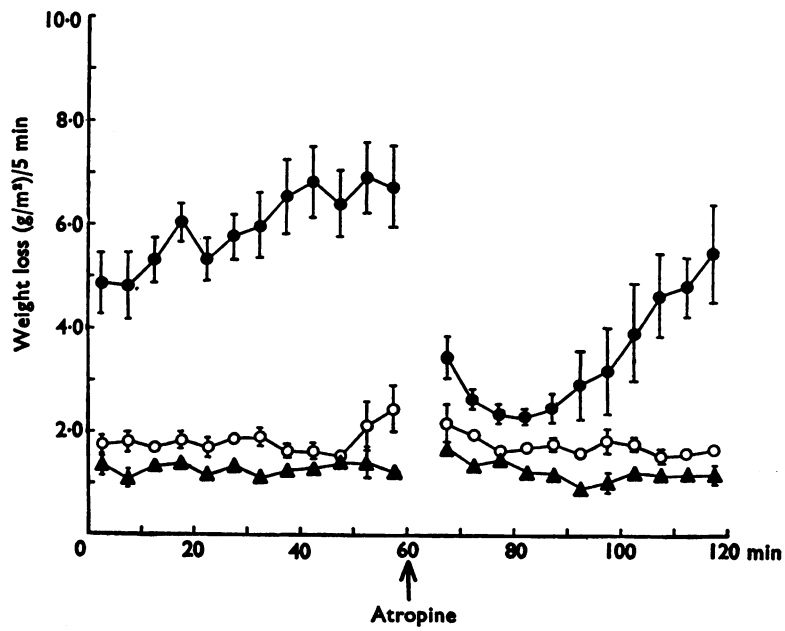

FIG. 4. The effects of atropine on the rate of weight loss of 4 subjects at environmental temperatures of 18°, 29° and 37° C. ●, 37° C; ○, 29° C; ▲, 18° C.

almost as steep as during the control period. In this subject, all the body temperatures rose slightly following the atropine injection.

The mean weight loss results for the 4 subjects at 37° C are shown in Figure 4. The mean control rate of weight loss for the 30 min before the injection was 6·5 (g/m²)/5 min (S.E. ±0·3). The mean rate for the 30 min following the injection was 2·7 (g/m²)/5 min (±0·2) and this was a significant decrease ($P<0·01$). The lowest mean rate of weight loss reached during any 5 min period after the atropine was 2·3 (g/m²)/5 min (±0.15). Towards the end of the experiment the rate of weight loss gradually increased, the final mean value being 5·4 (g/m²)/5 min (±1·0).

Heart rate was significantly increased ($P<0·01$) by atropine, rising from a mean control value of 81 beats/min (±1) to 116 beats/min (±1).

Mouth temperature rose significantly ($P<0·02$) after atropine from a mean control value of 37·0° C (±0·04) to 37·3° C (±0·1). Forehead skin temperature also rose significantly ($P<0·05$) from a mean control level of 36·6° C (±0·04) to 37·0° C (±0·1) after atropine. Hand skin temperature increased from a mean control level of 36·2° C (±0·1) to 36·8° C (±0·1).

In an enviromental temperature of 29° C injection of 2·4 mg of atropine had no effect on weight loss (Figs. 4 and 5). In Figure 5 there is no alteration in the

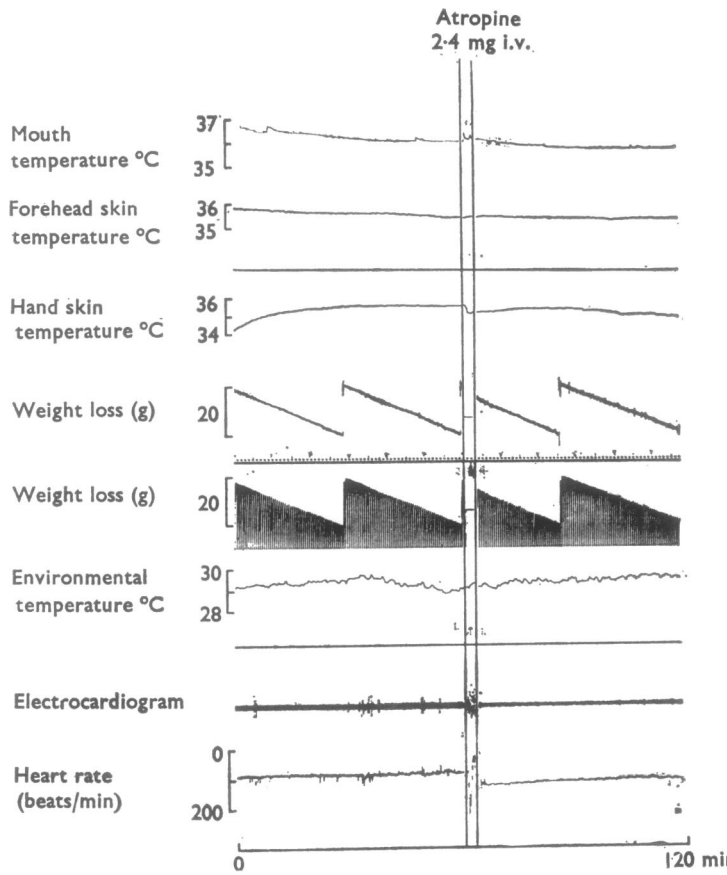

FIG. 5. The effects in one subject of injection of atropine in an environmental temperature of 29° C.

gradient of the weight loss slopes following injection of atropine. The mean control rate of weight loss for the 4 subjects was 1·8 (g/m²)/5 min (±0·1) and this was not significantly altered following treatment with atropine being 1·8 (g/m²)/5 min (±0·05).

Heart rate was again significantly ($P<0·01$) elevated by atropine from a control rate of 65 beats/min (±1) to 98 (±1), but there was no significant alteration in any of the body temperatures.

In an environmental temperature of 18° C, injection of atropine had no effect on the rate of weight loss (Fig. 4). The mean control rate of weight loss was 1·5 (g/m²)/5 min (±0·2) and was not significantly altered by atropine being 1·2 (g/m²)/5 min (±0·1) after the injection.

Heart rate was again significantly raised by atropine from a control rate of 58 beats/min (±1) to 113 (±3). Mean mouth, forehead and hand skin temperatures fell continuously throughout the experiments.

As can be seen from Fig. 4 following the administration of atropine, the residual rate of weight loss at 37° C was greater than that at 29° C which in turn was greater than that at 18° C.

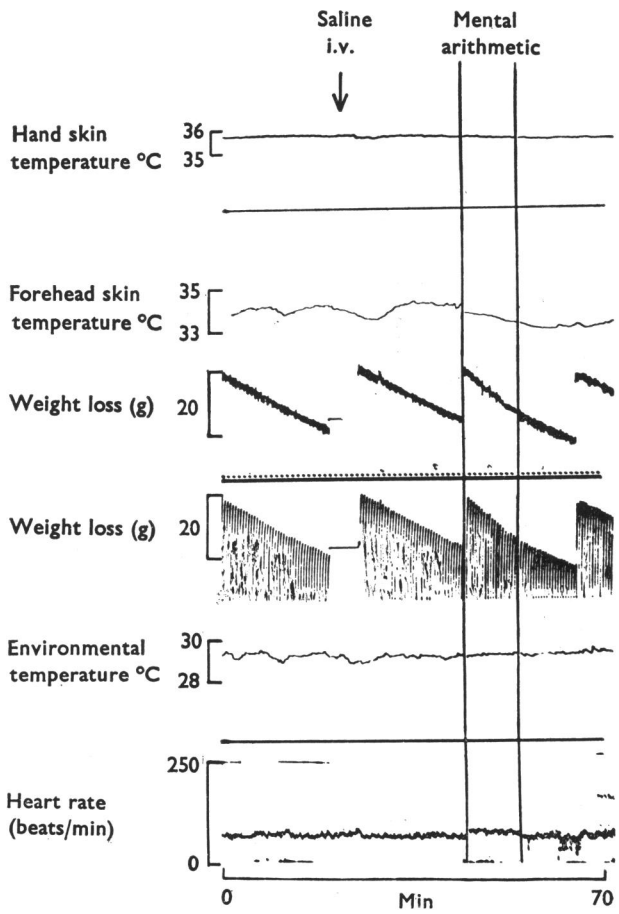

FIG. 6. The effects in one subject of 10 min of mental arithmetic.

Effects of propranolol on emotional sweating

Figure 6 shows the effect of mental arithmetic in one subject in an environmental temperature of 29° C. The rate of weight loss increased immediately after the onset of the mental stress and returned to control levels immediately the arithmetic was over and the subject relaxed again. Heart rate was elevated during the stress and hand skin temperature fell.

Figure 7 shows the results for the 6 subjects. After propranolol, the mean rate of weight loss during the stress reached a peak of 3·8 (g/m²)/5 min (±0·7) compared with a control level of 2·0 (g/m²)/5 min (±0·1). In the control experiments when saline was injected instead of propranolol, the response was not significantly different, the increase being from 1·9 (g/m²)/5 min (±0·1) to 3·8 (g/m²)/5 min (±0·2). These increases were significant at the 5% and 1% levels respectively.

After receiving an injection of saline, mean heart rate rose significantly ($P<0·01$) during the stress from a control level of 66 beats/min (±2) to a peak of 79 (±6). This increase was not seen when the stress followed injection of propranolol which itself significantly ($P<0·01$) lowered the resting heart rate from 73 beats/min (±2) to 60 (±4).

In the control experiments, hand skin temperature fell significantly ($P<0·02$) during mental arithmetic from a control level of 34·1° C (±0·1) to 33·7° C (±0·2). This significant decrease was not seen in the experiments with propranolol.

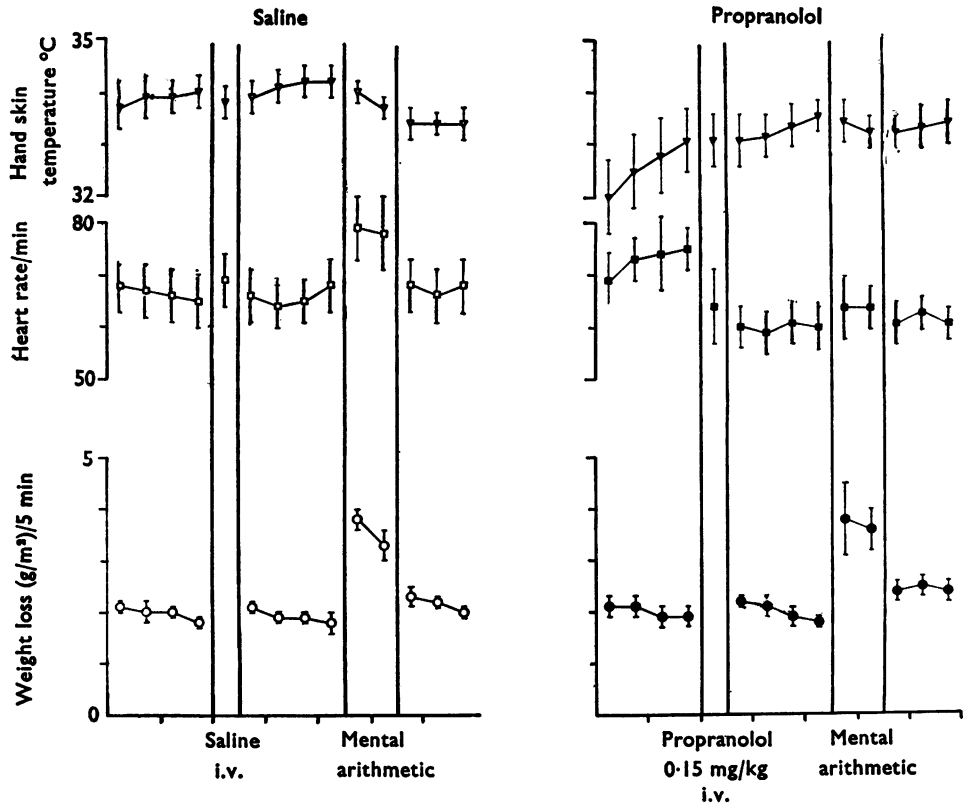

FIG. 7. The mean results of 12 experiments on 6 subjects exposed to a 10 min period of mental arithmetic after treatment with intravenous saline or propranolol.

Peak flow rates did not alter significantly in the subjects during an experiment in which they received a saline injection, but they were significantly decreased ($P<0.05$) after propranolol injection.

Discussion

Intravenous injection of propranolol during thermally induced sweating at environmental temperatures of 34° and 40° C had no effect on the rate of total body weight loss. The loss in total body weight measured was composed of respiratory and cutaneous water loss. As the subjects were at rest, respiratory water loss could be assumed to remain relatively constant and therefore any changes in the rate of total body weight loss could be attributed to changes in cutaneous water loss. Thus, it appeared that propranolol did not block thermal sweating in normal subjects. The dose of propranolol used is generally accepted as sufficient to produce widespread β-adrenoceptor blockade in man and in all these experiments significantly reduced resting heart rate in all the subjects.

Human sweating is known to be mediated by cholinergic sympathetic nerves (Chalmers & Keele, 1952; Kuno, 1956). The effect of atropine administration on cutaneous water loss in normal subjects under the experimental conditions was therefore studied at different environmental temperatures.

At 37° C, injection of atropine immediately greatly decreased the rate of weight loss (Figs. 3 and 4), in marked contrast to the negative effects of propranolol administration (Figs. 1 and 2). The large decrease in the rate of total body weight loss following injection of atropine is due to blockage of active sweating. The residual loss of weight is composed of respiratory water loss and the continuous passive diffusion of water outwards through the skin. These latter processes together comprise the insensible perspiration of the body. At 37° C, complete block of active sweating was apparently only achieved for a short time, during the 10 to 30 min period after the atropine injection. The rate of weight loss then began to rise again so that within 60 min of injection of atropine all the subjects were sweating freely once more. The dose of atropine used was a large one, well in excess of the normal clinically used doses. At the end of the experiments all the subjects appeared to be still well atropinized in other respects, heart rate was still elevated and showing little tendency to fall to pre-injection levels, salivation was still absent, and pupils were still widely dilated. The transient nature of atropine blockade of thermal sweating in the presence of a strong heat stimulus has been observed by other workers (Webb, Garlington & Schwarz, 1957; Craig & Cummings, 1965; Cummings & Craig, 1967) although the mechanism remains obscure. Foster & Weiner (1970) observed a similar effect in the cat's pad sweat glands when atropine completely blocked sweating due to plantar nerve stimulation at low frequencies but the sweat response recovered within a few minutes if the rate of nerve stimulation was high.

At 37° C, sweating is the only means of heat loss available to the subject and it is perhaps surprising that the mouth temperature did not rise more at this temperature following injection of atropine. The small size of the increase (from 37·0° C to 37·3° C) may be due to the transient nature of the atropine blockade of sweating.

In environmental temperatures of 29° and 18° C, injection of atropine did not significantly affect the rate of weight loss of the 4 subjects. These results suggest

that at these temperatures no active sweating was occurring and that the measured loss in total body weight was due entirely to insensible perspiration. These conclusions are in agreement with earlier reports that active thermal sweating occurs only at a certain level of thermal stress, usually reported as an environmental temperature in the region of 31° C (Ladell, 1945).

From the mean rates of weight loss following injection of atropine at 18° and 29° C it can be concluded that when at rest, rates of weight loss in excess of 1·2 (g/m^2)/5 min ($\pm$0·5) i.e. $\pm$2 S.D.'s at 18° C and in excess of 1·8 (g/m^2)/5 min ($\pm$0·4) at 29° C following any stimulus or procedure would suggest that active sweating had been precipitated by that event. At 37° C, rates of weight loss less than 6·5 (g/m^2)/5 min ($\pm$2·5) would suggest partial blocking of active sweating. A rate of weight loss close to 2·3 (g/m^2)/5 min ($\pm$0·4) at 37° C would suggest complete inhibition of sweating.

The experiments on emotional sweating were carried out in an environmental temperature of 29° C so that it could be assumed that no active thermal sweating was occurring. Although subjects were close to the thermal sweating threshold, control experiments indicated that the rate of weight loss at this temperature remains constant over a two-hour period. Mental arithmetic is a well recognized and convenient method of eliciting emotional sweating (Kuno, 1956).

In these experiments, the sweat response to mental arithmetic was not significantly altered by treatment with propranolol. Again the dose of the drug used should be sufficient to produce adequate β-adrenoceptor blockade and it did cause significant reductions in resting heart rate and peak flow rates in all the subjects. It also prevented the increase in heart rate during the mental stress which was apparent in the experiments where saline was injected instead of propranolol.

The cross-over design of the experiments was necessary since in trial experiments the response to mental arithmetic tended to decrease with repetition of the procedure as the subjects adapted to it.

Thus β-adrenoceptor blockade does not reduce either thermally or emotionally induced sweating in normal subjects. This is in contrast to the effects of cholinergic blockade. There is therefore no evidence from these experiments to suggest that the reported reduction in sweating in thyrotoxic patients treated with propranolol could be due to a direct action of the drug on the sweating mechanisms.

REFERENCES

ALLEN, J. A., GRIMLEY, J. F. & RODDIE, I. C. (1971). A body balance to measure sweat rates in man. *Biomed. Engng.*, **6**, 468–471.

ALLEN, J. A. & RODDIE, I. C. (1972). The role of circulating catecholamines in sweat production in man. *J. Physiol., Lond.*, **227**, 801–814.

BRICK, I., HUTCHISON, K. J. & RODDIE, I. C. (1970). Beta adrenergic blocking properties of D and DL propranolol in man. *Irish J. med. Sci.*, **3**, 123–130.

CHALMERS, T. M. & KEELE, C. A. (1952). The nervous and chemical control of sweating. *Br. J. Derm.*, **64**, 43–54.

CRAIG, F. N. & CUMMINGS, E. G. (1965). Speed of action of atropine on sweating. *J. appl. Physiol.*, **20**, 311–315.

CUMMINGS, E. G. & CRAIG, F. N. (1967). Influence of the rate of sweating on the inhibitory dose of atropine. *J. appl. Physiol.*, **22**, 648–654.

DE ELIO, F. J. (1948). Acetylcholine antagonists: a comparison of their action in different tissues. *Br. J. Pharmac. Chemother.*, **3**, 108–112.

DU BOIS, D. & DU BOIS, E. F. (1916). Clinical calorimetry. A formula to estimate the approximate surface area if height and weight be known. *Arch. Int. Med.*, **17**, 863–871.

ELWOOD, J. M. (1967). The cholinergic blocking properties of DL and D propranolol in normal and depolarised rat uterus. *Irish J. med. Sci.*, **6**, 327.

FOSTER, K. G. & WEINER, J. S. (1970). Effects of cholinergic and adrenergic blocking agents on the activity of the eccrine sweat glands. *J. Physiol., Lond.*, **210**, 883–895.

HEDGES, A. & TURNER, P. (1971). Effect of five β-adrenoceptor antagonists on the effects of isoprenaline and acetylcholine on human isolated smooth muscle. *Br. J. Pharmac.*, **41**, 426P.

JAMES, T. N. & NADEAU, R. A. (1963). Chronotropic and vagal blocking effects of DCI studied by direct perfusion of the sinus node. *J. Pharmac. exp. Ther.*, **140**, 73–78.

JAMES, T. N. & NADEAU, R. A. (1964). The chronotropic and vagal blocking actions of naphthyl-isoproterenol studied by direct perfusion of the sinus node. *J. Pharmac. exp. Ther.*, **143**, 350–355.

KRIKLER, D. M. (1966). Adrenergic receptor blockade. *Lancet*, **i**, 268.

KUNO, Y. (1956). *Human Perspiration.* Springfield: Charles C. Thomas.

LADELL, W. S. S. (1945). Thermal sweating. *Br. med. Bull.*, **3**, 175–179.

MORALES-AGUILERA, A. & VAUGHAN WILLIAMS, E. M. (1965). The effects on cardiac muscle of beta receptor antagonists in relation to their activity as local anaesthetics. *Br. J. Pharmac. Chemother.*, **24**, 332–338.

SHANKS, R. G., HADDEN, D. R., LOWE, D. C., MCDEVITT, D. G. & MONTGOMERY, D. A. D. (1969). Controlled trial of propranolol in thyrotoxicosis. *Lancet*, **i**, 993–994.

WEBB, P., GARLINGTON, L. N. & SCHWARZ, M. J. (1957). Insensible weight loss at high skin temperatures. *J. appl. Physiol.*, **11**, 41–44.

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