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BETA-ADRENORECEPTOR BLOCKADE ATTENUATES HEAT-INDUCED TACYCARDIA, BUT NOT THE TOLERANCE TO THE STRESS

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Abstract: Ten healthy males (age 34±3 yr 9 SE) underwent 40 min of heat exposure (WD 39.7•C) after 2 hours of ingesting 120 mg of Propranolol (Inderal; ICI), or a placebo, in a random manner, the exposures being about a week apart. That there was no placebo effect was ensured by giving a *control* run (no medication). In the placebo trials, the end-experiment heart rate had increased by 52%, while after propranolol the increase was only 43%. Regression analysis showed that with the placebo, the HR increased by 22 beats/min/° rise in core (aural) temperature, while with propranolol, the rise (14 beats/min) was significantly lower (P<0.02). The various heat strain indices viz. the Craig's Index, the Body heat storage (Kilocals/m²/hr), and the effective heat storage were also similar for both the treatments. We conclude that beta-adrenoreceptor activity plays a significant role in producing tachycardia of heat exposure in humans, but blocking this activity with propranolol does not affect tolerance to heat stress.

Key words: heart rate heat tolerance SA node

INTRODUCTION

Exposure to high environmental temperature results in tachycardia. The main reasons for this could be direct heating of the SA node by the warm blood bathing it (1); or modification of the autonomic influences on the SA node (2). In conscious baboons, exposed to a moderately severe heat stress, the extent of tacyhcardia reduced from 20 beats/min/°C increase in the core temperature to 13 beats/min after beta-adrenoreceptor blockade with propranolol (2), thus establishing that sympathetic activity of the SA node plays an important role in the causation of this tachycardia. In human subjects however, the role played by the beta-adrenergic receptor excitation of the CVS in producing heat induced tachycardia and other effects is controversial. Dikshit et al (3) postulated that sympathetically mediated excitation occured to produce cvs alterations during exposure to severe heat stress in normal subjects, while others (4) suggested that vagal tone withdrawal was an important contributory factor. In this study, we have given oral propranolol to normal human subjects to demonstrate that there is significant attenuation of heat induced tachycardia with the medication. We also hypothetised that betadrenoreceptor blockade may alter tolerance to heat stress adversely because it may reduce skin blood flow and sweating of the treated subjects.

METHODS

In a preliminary study, we treated eight healthy subjects with 120 mg propranolol (Inderal ICI; 40 mg tabs), and found that their mean resting heart rate had decreased from 70.4 ± 2.1 (SEM) beats/min to 58.4 ± 2.3 beats/min (P<0.01). For a given load of exercise on the treadmill (Venky, Madras) which resulted in a HR of 150 beats/min, administering propranolol decreased the HR to 105.5 ± 4.1 beats/min. This confirmed that 120 mg of oral propranolol did infact produce a physiologically significant beta-adrenergic receptor blockade.

Ten healthy male heat adapted subjects (mean age 34.1 ± 2.8 (SEM) yr; height 171.4 ± 1.69 cm and weight 65.8 ± 2.5 kg) volunteered for the study which

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was ethically approved. The subjects' consent was obtained, and their fitness to undergo the stress was ascertained by a medical examination.

The heat exposures were given in an Environmental Chamber (Kasco Industries) set to give a heat stress of Oxford Index 39.7°C (mean Dry bulb temperature 49.1°C, wet bulb 38°C, RH 50%). The average air velocity in the chamber remained at about 1m/sec.

The skin temperature was recorded using skin probes and an electronic digital six channel thermometer (Naina T 506) from four sites: the chest, right upper arm, right thigh (medial surface) and right calf to calculate the mean skin temperature (Tsk) (5). The aural (external auditary canal) temperature was also recorded to represent the Tcore (6) using the Naina equipment with a modified aural probe. The mean body temperature (Tmb) was calculated as 2/3Tcore + 1/3 Tsk (7). The heart rate was monitored continuously on a cardiac monitor (IndChem TruScope), and the blood pressure was measured using an aneroid sphygmomanometer. These variables were monitored from outside the chamber– prior to starting of the heat stress (0 min), and thereafter at 5, 10, 20, 30 and 40 min during the heat expsoure.

Seven of the subjects also marked their subjective discomfort on a 10 cm scale rated from no discomfort (0) to intolerable (100) at the 15th and the 30th min of heat exposure. Nude body weight was recorded before and after the heat stress to assess the degree of sweating. The obtained data was used to calculate various heat strain indices which were 1. the Modified Craig's Index (Is) (8); the Body Heat Storage Index (Qs) (9); the Effective body heat storage (Qe) and the Circulatory strain index (C) (10).

Protocol: Each subject, wearing an Air Force light weight overall (CL0 value 1) was exposed to the given heat stress (WD 39.7°C) for 40 min on three different occasions, with a 5-7 days interval between any two exposures. On one occasion, the subject ingested orally 120 mg of propranolol (Inderal; ICI) 2 hours before the heat stress, while on another he was given an equivalent amount of placebo. To confirm that the placebo effect was not present, he was also given a "control" heat exposure in which no medication was given. These runs were randomely administered in a single blind manner. All heat exposures were commenced at 1100 hours. All our subjects withstood the stress for the full 40 min.

Statistics: The Students paired T test was used to compare statistically the values of the physiological variables recorded, and the change in these values produced by the heat exposure in the control and the placebo runs, with $P< 0.05$ being the level of significance. As there was no difference between these (see Results), it was decided that there was no *Placebo effect,* and thereafter the paired t test was used to compare the variables, and the changes in the variables (control to terminal (end of 40 min of exposure) for the placebo and the propranolol exposures. Similar comparison was made between the heat strain indices measured.

The regression coefficient for the HR per degree rise in the Tcore was determined using a PC and a Lotus 123 worksheet which computed the value from the given data.

RESULTS

That adequate beta-adrenergic receptor blockade had occured after the given oral dose of propranolol (120 mg) was demonstrated by the fact that the pre-heat exposure HR for the placebo experiments was 67.1 ± 1.9 (SEM) while for the propranolol exposures it was 55.9 ± 2.1 beats/min ($P< 0.01$). At the end of the heat exposures, the "placebo HR" had increased by 34.1 ± 2.9 beats/min (51.9 ± 4.3%) while the "propranolol HR" had increased by 23.8 ± 2.6 beats/min (42.9 ± 4.9%). Both, the absolute and the % increases were statistically lower for the propranolol experiments ($P< 0.01$ and <0.02 respectively). The overall HR, mean arterial pressure (MAP mmHg) and body temperature response during the 40 min of heat exposure is given in Table I. The comparison for the change from control at the end of 40 min of heat exposure for the two experimental conditions is given in Table II.

TABLE I : Depicts mean and SEM values for heart rate (HR; beats/min), mean arterial pressure (MAP; mmHg), core temperature (Tcore°C) and the skin temperature (Tskin°C) in 8 subjects exposed to a WD of 39.7°C for 40 min after having consumed either 120 mg of Placebo (PL) or propranolol (PR).

Time min		*HR/min*	*MAP mm Hg*	*T Core °C*	*T skin °C*
0 min	P1	67.1 (1.2)	85.9 (2.8)	36.86 (0.15)	34.56 (0.17)
	Pr	55.9 (2.1)	83.1 (2.3)	36.51 (0.16)	34.34 (0.10)
5 min	P1	77.4 (1.9)	83.2 (2.8)	37.65 (0.13)	36.67 (0.23)
	Pr	63.0 (2.6)	78.8 (2.4)	37.34 (0.22)	36.31 (0.18)
10 min	P1	81.0 (2.4)	80.1 (3.0)	37.90 (0.07)	37.35 (0.16)
	Pr	65.4 (2.4)	76.4 (2.7)	37.64 (0.23)	37.08 (0.14)
20 min	P1	87.1 (2.8)	80.5 (2.8)	38.18 (0.07)	38.09 (0.07)
	Pr	72.3 (2.8)	76.5 (2.5)	37.89 (0.27)	37.94 (0.08)
30 min	P1	96.0 (3.2)	79.3 (2.5)	38.30 (0.08)	38.36 (0.08)
	Pr	75.5 (3.4)	76.8 (2.6)	38.18 (0.25)	38.29 (0.04)
40 min	P1	100.1 (3.7)	79.4 (2.7)	38.56 (0.11)	38.72 (0.11)
	Pr	79.6 (3.5)	77.0 (2.9)	38.36 (0.24)	38.64 (0.03)

TABLE II : The mean (SE) change, and percentage change (between control values and the 40 min values) for heart rate (beats/min) (HR); the mean arterial pressure mmHg (MAP); the core temperature °C (TC); and the mean skin temp °C (Tsk) of 8 subjects for placebo (PL) and propranolol (PR) experiments. Sig is stat. significance.

	Absolute change		*sig.*	*% change*		*sig.*
	PL	*PR*		*PL*	*PR*	
HR	34.1 2.9	23.8 2.6	P< 0.01	51.9 4.3	42.9 5.0	P<0.02
MAP	6.2 2.2	6.1 2.1	NS	6.9 2.5	7.3 2.5	P<0.05
Tc	1.8 0.2	1.9 0.2	NS	4.8 0.4	5.1 0.5	NS
Tsk	4.1 0.2	4.3 0.1	NS	12.4 0.4	12.5 0.3	NS

(In the final analysis, data from 2 of the subjects (nos. 3 and 7) had to be rejected because their temperature measurements were found to have gone awry.

The regression coefficient for the HR/° rise in the Tcore for the propranolol trials was 13.8 ± 2.2 (SEM), which was significantly lower (P< 0.01) than the regression coefficient value for the placebo experiments (21.8 ± 3.3). The overall relation is shown in Fig. 1.

The sweat rate (kg/hr) for the propranolol and the placebo runs was similar (0.621 ± 0.075 and 0.664 ± 0.093 respectively).

The heat strain indices calculated from the various physiological variables recorded are given in Table III. Only the Circulatory strain index (C) for the propranolol trials was significantly lower (P<0.01).

The extent of subjective discomfort as indicated by the VAS *(Visual assessment scores)* at 15 and 30 min for the placebo and propranolol experiments were 27% and 25% at 15 min, and 62.2% and 61.6% at 30 min respectively (NS).

TABLE III : Depicts the mean and SEM values for the Modified Craig's index (Is, units), the Body Heat Storage index (Qs; kilocals/m²), the Effective Body Heat Storage index (Qe; kilocals/m²), and the Circulatory strain index (C; units) in 8 subjects exposed to WD 39.7°C for 40 min after oral ingestion of 120 mg Placebo (PL) or Propranolol (PR).

	Is	*Qs*	*Qe*	*C*
Placebo	4.21 0.17	118.3 6.8	33.4 5.0	2870.3 322.9
Propranolol	4.20 0.25	123.2 4.8	39.4 2.9	1590.2 213.4
P-Pl vs Pr	NS	NS	NS	<0.01

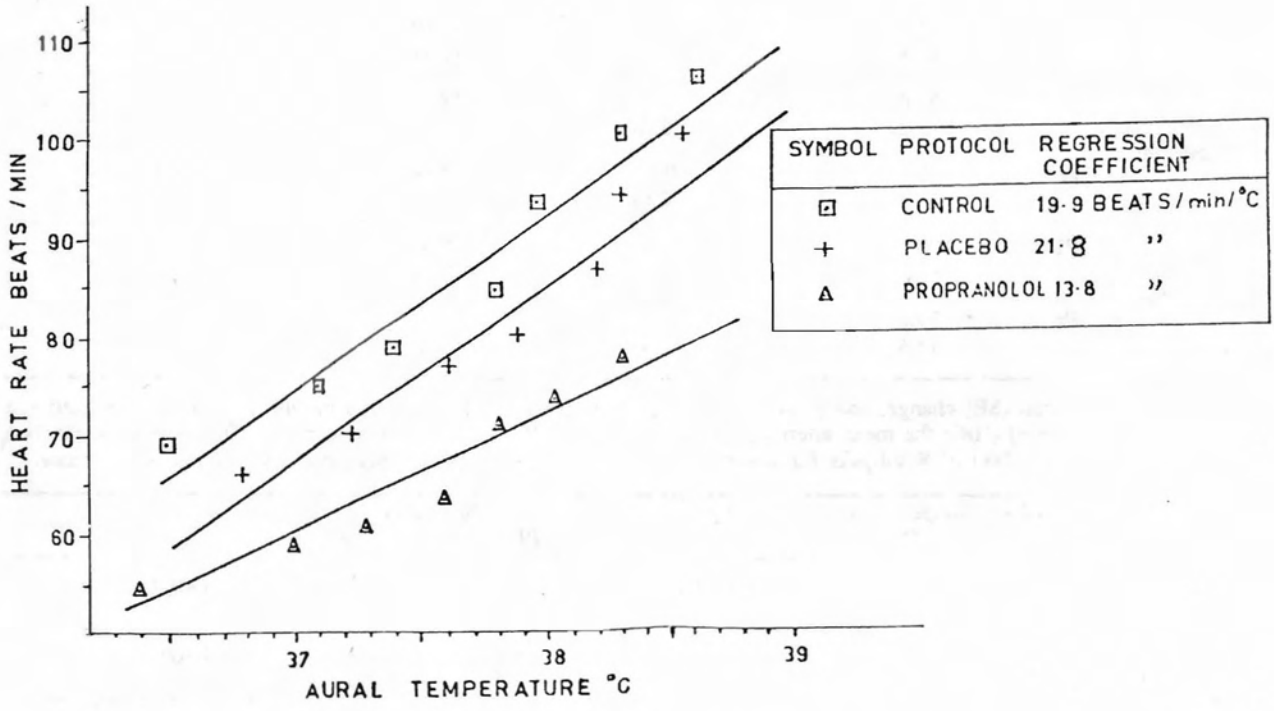

Fig. 1: The HR response to increasing core temperature in the three experimental situation.

DISCUSSION

Oral ingestion of 120 mg Propranolol produces significantly effective beta-adrenoreceptor blockade after 2 hours (11). We confirmed this in a separate study in 8 different subjects (see methods). Also, in this study, the 2 hour post propranolol HR was significantly less as compared with the post placebo HR (Table I- 0 min HR). We were therefore convinced that physiologically significant beta-adrenoreceptor blockade had been produced in our subjects with the given oral dose of propranolol. Intra-venous (iv) propranolol was not used because in the actual heat stress conditions in military and industrial situations, the subjects would be on oral medication. Also, our laboratory was not equipped to treat accidental cardiac arrests which may occur with iv propranolol infusion.

In conscious baboons, about 60% of the heat induced tachycardia has been attributed to autonomic innervation of the heart (2). Also the heat induced tachycardia of 20 beats/min/°C rise in the Tcore in baboons reduced to 13 beats/min after iv propranolol. In unanaesthetised dogs exposed to 50°C for 30 min, beta-adrenoreceptor blockade reduced the HR from 157 beats to 128 beats (12). Thus in the unconscious animal models beta-adrenergic stimulation at the SA node contributes significantly to the heat-induced tachycardia. The status of this phenomenon in human subjects however is ill defined.

Berlye et al (13) used beta-adrenergic blockade with iv propranolol in their human subjects during heat exposure. They found that the exercise heart rate with treatment was less, but that the body temperature control was not adversely affected. But the stress used for this study), was relatively mild (WD 28°C as against the 39.7°C in this study), and the subjects exercised during the heat stress. Therefore the end result was produced by a combination of two stresses acting simultaneously. Their conclusions on HR response therefore can not be applied to the situation used in the present study.

We report here that the heat-tachycardia response of normal heat adapted human subjects [21.8 beats/min/°C increase in the core temperature - similar to the response of baboons (2)] was significantly attenuated to 13.8 beats/min after 120 mg of oral propranolol ingested 2 hours prior to the heat exposure. Thus a tachycardia of about 8 beats/min is attributable to beta-adrenoreceptor influence. It could be argued that our results may in fact underestimate the role of the beta-adrenoreceptor stimulation in producing heat-tachycardia because we used the oral and not the iv preparation, and hence did not obtain complete beta blockade. However our beta-blocked HR response values are close to those reported for conscious baboons given iv medication (2). That the beta-blockade in our subjects was significant has been established (earlier part of the discussion).

Jose et al (1) have reported that an increase of about 7.2 beats/min/°C increase in core temperature during heat expsoure of human subjects is attributable to a direct heating of the SA node. Applying this data to our study, out of a tachycardia response of 21.8 beats/min/°C in heat, 14.6 beats/min can be attributed to autonomic nervous control readjustments of the SA node, amounting to 67% of the tachycardia. This figure is close to the 60% autonomic influence reported for baboons (2). Of the autonomic control, 8 beats/min are attributed to beta-adrenoreceptor influence. This constitutes 54.8% of the autonomic control, and 36.7% of overall tachycardia response. Therefore we have established that beta-adrenoreceptor stimulation plays an important role in producing heat induced tachycardia during whole body heating in normal heat-adapted humans. We did not attempt to assess the role of vagal control withdrawal in this tachycardia because (i) this was beyond the scope of this limited study and (ii) we did not treat our subjects with iv atropine because of ethical considerations.

It may be that arterial baroreceptor deactivation occurs during heat exposure (14) because there is some fall in the mean arterial pressure (MAP, mmHg) attributed to the vasodilatation of the skin blood vessels. This may then contribute to a reflex tachycardia. In our study, the MAP fell by about 6 mmHg (for both the placebo and the propranolol experiments), in the first 10 min or so, and stabilised thereafter, while the HR continued to increase. Therefore arterial baroreceptor deactivation did not contribute to the heat induced tachycardia. Our observations support those made earlier (15, 16).

It may be argued that in some military and industrial situations, subjects on medication with beta-adrenoreceptor blockade may be exposed to moderately severe heat stress as a part of their routine duties. Such subjects may be at a disadvantage because their tachycardia response is attenuated, and this may in fact reduce their tolerance to heat stress (10). Also, apart from affecting heart rate response, propranolol may affect sweating adversely because eccrine sweat glands have cholinergic and adrenergic innervation (17). When there is simultaneous stimulation of both, sweating is most effective, and therefore, if adrenergic blockade is given, sweating may reduce (17). Gordon (18) however has reported that there was a slight increase in sweating after propranolol administration. In the present study, sweat loss in the placebo and treated subjects was similar.

Prescatello et al (19) have presented evidence that propranolol affects thermoregulation, and concluded that a reduction in the skin blood flow of propranolol treated subjects probably produced this effect. There was no significant difference in the body temperatures of the subjects, whether treated or untreated with the beta-blocker (Table I). We could not measure skin blood flow. Further, all the heat strain indices calculated from the physiological data obtained (except for the Circulatory strain) was similar for both the protocols (Table III). The latter was expected as this index is based entirely on the HR. (The disadvantage of using only a single index in assessing the degree of heat strain is adequately brought out here). Subjectively, the VAS scores at 15 and 30 min of heat expsoure were similar for both the protocols, thereby establishing that propranolol did not affect adversely the degrees of subjective discomfort felt by the subjects.

From the study it is concluded that (i) beta-adrenoreceptor stimulation contributes substantially to the tachycardia response of whole body heating, and (ii) beta-blockade does not adversely affect tolerance to moderately severe heat stress. The findings have an important bearing on the employability of military and industrial personnel in conditions of moderately severe heat stress.

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