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EFFECT OF MODAFINIL ON HEAT PRODUTION AND REGULATION OF BODY TEMPERATURES IN COLD-EXPOSURE HUMANS

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Effect of Modafinil on Heat Production and Regulation of Body Temperatures in Cold-Exposed Humans

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Military personnel often undergo sustained operations that affect vigilance and alertness. Pharmacological agents may be used to enhance vigilance. Most such agents also have thermogenic properties. Whether a new promising stimulant, modafinil (Lyons and French, Aviat. Space Environ. Med. 1991; 62:432–435), has a beneficial effect on cold tolerance in the military context, is not known. The goal of this study was, therefore, to evaluate the effect of this new drug on thermal balance and the regulation of body temperatures in neutral conditions and when challenged by a cold exposure. Nine subjects underwent three trials each: two in the cold (3 h at rest, 10°C) 0.5 h after the ingestion of either placebo or modafinil (200 mg), and one in thermal neutrality with modafinil (same conditions except T_{db} = 29.3°C). As expected, cold produced a drop in T_{re} and $\bar{T}_{sk}$ and an increase in $\dot{V}O_2$. Although non-significant, there was a tendency for a slightly greater drop in T_{re} with modafinil (0.65°C vs. 0.57°C with placebo). A similar tendency was found for the heat debt (S) which was greater with modafinil than with placebo (16.1 ± 0.7 vs. 14.7 ± 0.6 kJ · kg^{-1}, respectively, +9.5%, p = 0.11). This tendency appears to be the combined result of a slightly lower mean heat production during the test and a slightly greater mean dry heat loss. When tested at thermal neutrality, the drug had no effect on any thermal or metabolic parameters. The results demonstrate that the ingestion of a single dose of modafinil has no significant acute effect on thermal balance in neutral conditions and on thermoregulation in normal subjects exposed to cold. However, a tendency for slightly greater cooling was noted with modafinil. It is not known whether the use of modafinil in conjunction with sleep deprivation (a likely scenario) could magnify this effect.

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MILITARY PERSONNEL are often required to perform very long or even multiple extended missions, with or without brief periods of rest. Such sustained operations (SUSOP's) can have a detrimental effect on vigilance, alertness, and mood (8). Several countermeasures have been proposed to alleviate these detrimental effects of SUSOP's. Appropriate work/rest scheduling is the most obvious measure to consider, but its use is limited when there is no rest period during the mission or the subject's circadian rhythm for vigilance does not fit with the mission schedule. In these cases, using hypnotics or stimulants would appear quite attractive. Hypnotics can induce sleep and/or increase its quality when it is possible. When sleep is not possible, as in SUSOP's, stimulants can be used (5,11,12).

There is general agreement that the brain sleep-wake and thermoregulating mechanisms are closely related (1,9). Whether the same mechanisms are also equally affected by stimulant drugs is not known. What is known, however, is that both amphetamines (6,13) and the combination of methyl-xanthines β-adrenergic agonists (ephedrine and caffeine, 18,21), used for a long time for their psycho-stimulant activity (22), do increase metabolic heat production at rest in humans in neutral and cold conditions. This effect was reported to be sufficient to delay the onset of hypothermia in cold-exposed humans (18,21).

In a recent review, Lyons and French emphasized the "unique properties" of a new stimulant, benzhydrylsulfinylacetamide, namely modafinil (10). Whether modafinil has an influence on thermoregulatory thermogenesis or regulation of body temperatures is not yet known, but because of its potential for future widespread use, the effects on thermoregulation would be worthwhile to study.

The aim of this study was, therefore, to determine whether modafinil, at the normal acute dosage used to

improve alertness and vigilance, can enhance cold resistance in humans, and whether it does so through alterations in heat production or heat loss. This was accomplished by determining not only thermoregulatory thermogenesis as well as core and mean skin temperatures, but also by performing a full heat balance analysis, by calculating rates of energy substrate oxidation and by measuring levels of various plasma substrates and hormones, as indices of energy substrate mobilization.

METHODS

Subjects

Nine healthy male volunteers participated in the present study, which was approved by the institutional human ethics committee. Female subjects were not recruited for this experiment because the body temperature fluctuations associated with the menstrual cycle might have precluded completion of the experiment in the allocated time framework; we acknowledge that our conclusions may not be applicable to females until similar experiments are done with a female subject sample. Each subject was examined by a physician who approved his participation. The nature, purpose, and possible risks of the study were explained in detail to each individual before he gave his consent to participate. All subjects could withdraw from the study at any time without bias. Their physical characteristics are summarized in the results section.

Experimental Protocol

Before the test, each subject performed a 90-min familiarization run in the cold. Three 3-h tests were performed about 1 week apart on each subject: two in cold air (10°C), with either modafinil or placebo, and one in neutral condition (29.3°C) with modafinil. Each subject served as his own control, and the experiment was performed under double blind conditions. The placebo consisted of a gelatin capsule containing 0.36 g of an artificial sweetener (Nutrasweet®) to approximate the weight of the modafinil capsule. A similar capsule was used for the administration of modafinil. The order of tests was balanced to avoid any order effect. Dosage (200 mg) and schedule of the experiment were chosen according to the recommendations of Laboratoires L. Lafon (Maisons-alfort, France), and available pharmacological information (10,14).

The three tests took place in the same environmental chamber where subjects were sitting at rest in the same location in the chamber during all trials. They were wearing jogging shorts and foam slippers. Ambient temperature was controlled to within 0.1°C and wind speed was maintained below 0.4 $m \cdot s^{-1}$. Subjects were asked to avoid drinking alcohol for at least 48 h prior to the test, to refrain from heavy exercise in the 24 h prior, and to report to the laboratory in a fasting state (only water for 12–14 h).

Experimental Session

Fasting subjects reported to the laboratory in the early morning, and emptied their bladders. They self-inserted their rectal probes (Sherigan, Argyle, NY), and thereafter they were instrumented with an indwelling IV catheter in the forearm, 12 calibrated heat-flow transducers (Concept Engineering, San Diego, CA), and heart-rate monitors (Polar 3000, Polar USA, Stanford, CT). After ingesting their capsules, they were allowed to sit and rest quietly in the subject preparation room (22°C) for 30 min.

Just before entering the chamber, blood was sampled through the catheter (t_0), then the subject was wheeled (on the same chair) into the climatic chamber.

The test was terminated if: a) rectal temperature dropped below 35.0°C; b) the subject wished to withdraw from the test; or c) after 3 h of exposure. As soon as possible after the end of the cold tests, active rewarming was provided by immersion in a whirlpool bath at about 39°C. Subjects were allowed to empty their bladder after 90 min in the chamber ("urine break") and were required to do so at the end of the test.

Measurements

During the tests, rectal temperature (T_{re}) was used as an index of core temperature, and was monitored using a thin thermistor probe inserted 10 cm beyond the anus. Skin temperatures and dry heat loss were measured with 12 heat flow transducers (see above) taped to the skin. Using a 12-point area-weighed system, mean skin temperature ($\overline{T}_{sk}$) and mean dry heat loss were calculated as described elsewhere (19). All thermal data were continuously recorded by a computerized Hewlett-Packard 236 data acquisition system (19).

To allow continuous monitoring of metabolic heat production (M), two separate metabolic carts were used. Subjects were not switched from one system to another. The carts were a Beckman Horizon (Anaheim, CA), and an Ametec system consisting of an IBM PC with a polarographic O_2 (S-3A/I) analyser and an infrared CO_2 (CD-3A) analyser (Applied Electrochemistry, Pittsburgh, PA), a ventilation module (Interface Associates, Irvine, CA), and a Turbofit A/D computer interface (Vacumetrics, Ventura, CA). Expired gases were continuously sampled via a face mask (Hans Rudolph Inc, Kansas City, MO), except during the 5 min "urine break" at minute 90. Analyzers were calibrated before and, if required, during the tests.

Thermal and Metabolic Calculations

The heat balance equation summarizes whole-body heat exchanges in terms of not only heat production but also in terms of the various avenues of heat loss (16,20). It is described below:

$$M - W - (R + C) - E_{persp} - C_{resp} - E_{resp} - K - S = 0 \quad \text{Eq. 1}$$

where M is the average metabolic rate (calculated as previously described from $\dot{V}O_2$) and non-protein respiratory exchange ratio (NPRER) as previously reported (17); W is the external work rate (assumed to be nil here); R + C is the dry exchange of heat (measured); E_{persp} is the evaporative heat loss from the skin via cutaneous perspiration (calculated); C_{resp} is the convective heat loss by the respiratory tract (calculated); E_{resp} is the evaporative heat loss by the respiratory tract (calcu-

lated); K is the conductive heat loss (assumed to be negligible in this study); and S is the change in body heat content (calculated as the balance of heat gain and heat loss). Every term was expressed in $W \cdot m^{-2}$ of body surface area (bsa).

S can be positive or negative (in which case it represents a heat debt). It is calculated by rearranging Eq. 1:

$$S = M - (R + C) - Eresp - Cresp - Eresp \qquad \text{Eq. 2}$$

The average heat storage rate (S, $W \cdot m^{-2}$) was calculated every minute and the cumulative heat debt from minute 0 to minute k (S_k, $kJ \cdot kg^{-1}$) was then obtained by the following equation:

$$S_k = (60 \cdot \sum_{i=1}^{i=k} S_i) \cdot bsa \cdot weight^{-1} \qquad \text{Eq. 3}$$

Plasma Hormones and Substrates

Blood was drawn from the indwelling IV catheter at about 5 min prior to the test, in the chamber at minute 60 and minute 120, and at the end of the test. Plasma was assayed for glycerol, free fatty acids, (Wako Chemicals NEFA kit, Dallas, TX), glucose (YSI Instruments glucose kit), insulin (Kabi Pharmacia Diagnostics Insulin RIA 100 kit, Uppsala, Sweden), and glucagon (Diagnostic Products Corporation kit, Los Angeles, CA).

Statistics

The main effect of time and treatments as well as the time versus treatment interactions were tested by analysis of variance for repeated measures (ANOVA) (Biomedical Computer Programs, BMDP-90, Los Angeles, CA). ANOVA were corrected by the Huynh-Feldt epsilon adjusted degrees of freedom when the sphericity test was significant (BMDP-90). When interactions of effects were significant, paired *t*-tests (adjusted for multiple comparisons) were used to locate significant differences (set at $p < 0.05$). Results are expressed as mean ± standard error of mean (SEM).

RESULTS

Mean values (±SEM) for some physical characteristics of the subjects were as follows: age was 33.6 ± 1.2 years, height was 177 ± 2 cm, weight was 81.7 ± 2.6 kg, body fat percentage was 16% ± 2%, and treadmill $\dot{V}O_{2max}$ was 46 ± 1.1 $ml \cdot min^{-1} \cdot kg^{-1}$.

No significant changes in any variables were observed during the neutral environment test (Table I). All subjects were able to complete the 3-h cold-test in both placebo and modafinil conditions. Pre-test thermophysiological state of the subjects was quite similar for both tests (T_{re} = 36.97 ± 0.08 vs. 36.96 ± 0.06°C and $\overline{T}_{sk}$ = 32.0 ± 0.19 vs. 31.9 ± 0.20°C for placebo and modafinil, respectively) (Fig. 1).

As expected, cold had a significant effect on T_{re} and $\overline{T}_{sk}$ (time effect), but neither a treatment effect nor an interaction between treatment and time were observed on these variables (Fig. 1). Nevertheless, a tendency for a greater drop of both variables during the test with modafinil can be seen: ΔT_{re} was 0.57 ± 0.09 vs. 0.65 ± 0.13°C (+14%) and $\Delta \overline{T}_{sk}$ was 7.47 ± 0.45 vs. 7.60 ± 0.38°C (+2%) with placebo and modafinil respectively ($p = 0.20$ and $p > 0.50$, respectively).

The same observation can be made about the heat debt, which was slightly higher with modafinil than with placebo ($p = 0.11$) (Fig. 2). At the end of the tests, S_{180} differed by 9.5% between the two experimental conditions: 14.7 ± 0.6 vs. 16.1 ± 0.7 $kJ \cdot kg^{-1}$ for placebo and modafinil, respectively. The tendency observed in S can be analyzed using the procedure described above (Eq. 2). It appears to be related to both a slightly higher skin heat loss during tests (133.3 ± 2.6 and 6.1 ± 0.3 vs. 135.6 ± 3.2 and 6.5 ± 0.4 $W \cdot m^{-2}$ for dry heat loss, $p > 0.20$, and E_{persp}, $p > 0.25$, in placebo and modafinil, respectively) and a slightly lower level of metabolic heat production (81.6 ± 4.7 vs. 79.4 ± 4.8 $W \cdot m^{-2}$ in placebo and modafinil, respectively, $p = 0.30$) (Fig. 3b).

An important effect of time was observed on NPRER, which decreased during the cold test. Though the effect of treatment is not significant, the tendency for a higher NPRER with modafinil can be seen (0.859 ± 0.015 vs. 0.879 ± 0.020 with placebo and modafinil, respectively, $p = 0.07$). This difference seems to be related to a lower rate of fat oxidation with modafinil: 0.104 ± 0.012 vs. 0.091 ± 0.016 $g \cdot min^{-1}$ during placebo and modafinil tests, respectively, $p = 0.07$; carbohydrate oxidation was similar for both tests (0.273 ± 0.037 vs. 0.290 ± 0.043 during placebo and modafinil tests, respectively.

Plasma glycerol and FFA concentrations were significantly affected by a main effect of time but not by a main effect of treatment. Glucose concentration was not affected. Insulin decreased significantly with time in the cold, but there was no effect of treatment or interaction; glucagon was unaffected by both time and treatment.

DISCUSSION

The results demonstrate that under the present conditions modafinil does not improve the tolerance of humans exposed to a mild cold stress. Moreover, the results suggest that modafinil may induce a slight deterioration of cold tolerance, reflected in the following observations. The mean metabolic rate tends to be slightly lower during the modafinil test than during the

TABLE I. SELECTED THERMAL AND METABOLIC RATE VARIABLES DURING THE THERMONEUTRAL TEST (n = 9).

	Min t_o	Min t_{60}	Min t_{120}	Min t_{180}
T_{re} (°C)	39.9 ± 0.1	36.7 ± 0.1	36.9 ± 0.0	37.0 ± 0.0
$\overline{T}_{sk}$ (°C)	32.7 ± 0.1	33.5 ± 0.1	33.6 ± 0.1	33.7 ± 0.1
$\dot{V}O_2$ ($L \cdot min^{-1}$)	0.26 ± 0.01	0.27 ± 0.02	0.28 ± 0.02	0.30 ± 0.02
NPRER*	0.87 ± 0.02	0.92 ± 0.04	0.85 ± 0.03	0.82 ± 0.02

* NPRER refers to the calculated nonprotein respiratory exchange ratio.

TABLE II. AVERAGE PLASMA CONCENTRATIONS OF VARIOUS SUBSTRATES AND HORMONES DURING COLD EXPOSURE TESTS IN PLACEBO (P) AND MODAFINIL (M) CONDITIONS.

		Min t_0	Min t_{60}	Min t_{120}	Min t_{180}	
Glycerol	M	0.039 ± 0.003	0.078 ± 0.010*	0.103 ± 0.100*†	0.108 ± 0.011*†
(mM)	P	0.044 ± 0.004	0.072 ± 0.011*	0.103 ± 0.009*†	0.108 ± 0.010*†
FFA	M	109 ± 12	159 ± 19*	185 ± 19.2*†	197 ± 21*†
($mg \cdot L^{-1}$)	P	113 ± 11	172 ± 19*	198 ± 13*†	217 ± 16*†
Glucose	M	5.0 ± 0.1	4.9 ± 0.1	4.9 ± 0.1	4.9 ± 0.1
(mM)	P	5.0 ± 0.1	4.9 ± 0.1	5.0 ± 0.1	5.0 ± 0.1
Insulin	M	69 ± 11	58 ± 8	49 ± 7*	45 ± 5*†
(pM)	P	62 ± 9	56 ± 6	54 ± 7	47 ± 5*
Glucagon	M	102 ± 3			108 ± 5
($ng \cdot L^{-1}$)	P	109 ± 5			111 ± 7

Statistical significance at $p < 0.05$: * different from t_0, † different from t_{60}. There was no difference between P and M for any of these varaibles.

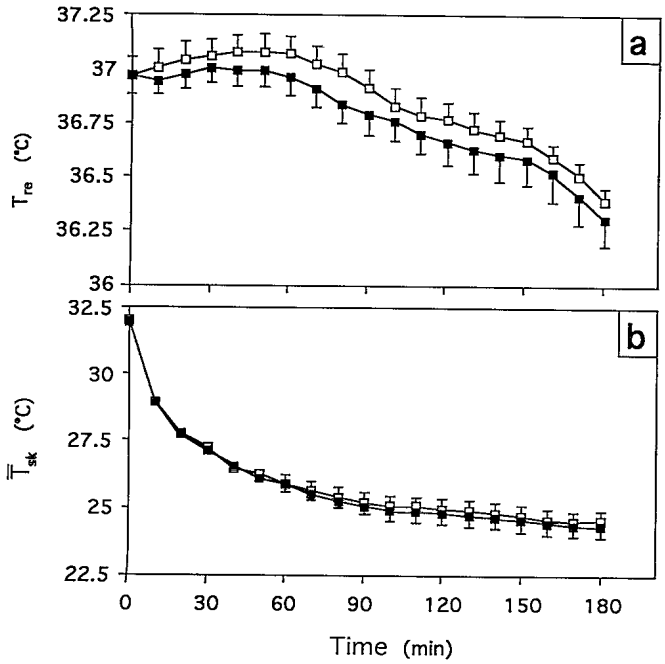

Fig. 1. a) Rectal temperature (T_{re}) and b) mean skin temperature (T_{sk}) for both placebo (□) and modafinil (■) treatments during the cold-exposure tests. Each point is the average of 10 min (except at t_0 and t_{180}) for the nine subjects (±SEM). There is no statistical difference between conditions.

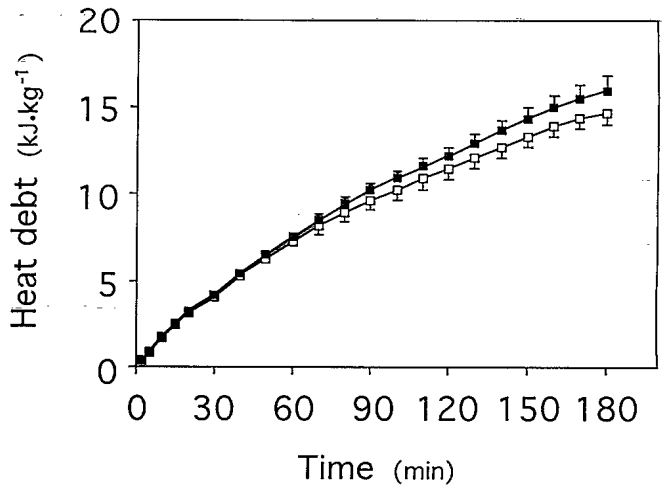

Fig. 2. Heat debt (S) time-course in both conditions: placebo (□) and modafinil (■), during the cold-exposure tests. Each point is the average of 10 min for the nine subjects (±SEM). There is no statistical difference between conditions.

placebo test. This tendency for a decrease in mean heat production during the modafinil test is partly explained by a lower fat oxidation rate (difference of about 12%, $p = 0.07$) without a compensation in carbohydrate oxidation. The reason for this difference in metabolism is not clear since there is no difference in the insulin or glucagon kinetics between the tests.

A very slight increase in mean heat loss was also noticed during the modafinil test, essentially provided by an increase in dry heat loss. This effect is difficult to explain. Nevertheless, in the cat, brain temperature (caudate nucleus) increases by more than 0.5° 2 h after an acute oral administration of the same dosage of modafinil (9). Such a direct effect on thermoregulatory centers could activate heat loss mechanisms and would, thus, be in line with the observed dry heat loss difference, at the same level of stimulus.

Taken together, the slight decrease in metabolic heat production and the slight increase in heat loss explain the difference in heat debt at the end of the tests (9.5%) and that the ANOVA analysis treatment factor for this parameter is not quite significant ($p < 0.11$). This tendency is reflected in the decrement in T_{re} during the test: 14% higher at the end of the modafinil test than at the end of the placebo test.

This unexpected reaction is certainly not due to a pharmacodynamic effect, since modafinil was administered at the dose recommended to improve vigilance and alertness in healthy subjects (10,14). Also, measurements were made continuously from 30 min to 3.5 h after the subjects ingested the pill, finishing closer to the peak of vigilance enhancement (reported to be at the 4th hour in humans under these conditions, 14). Moreover, there is no time course argument to assume that a difference in the other direction would appear if the tests had been prolonged (Fig. 3b).

The hyperthermic action of amphetamines is described to be acute and short (6). Its mechanism is not yet well understood, but could be partly attributed to a peripheral action of these drugs (4). The recent finding

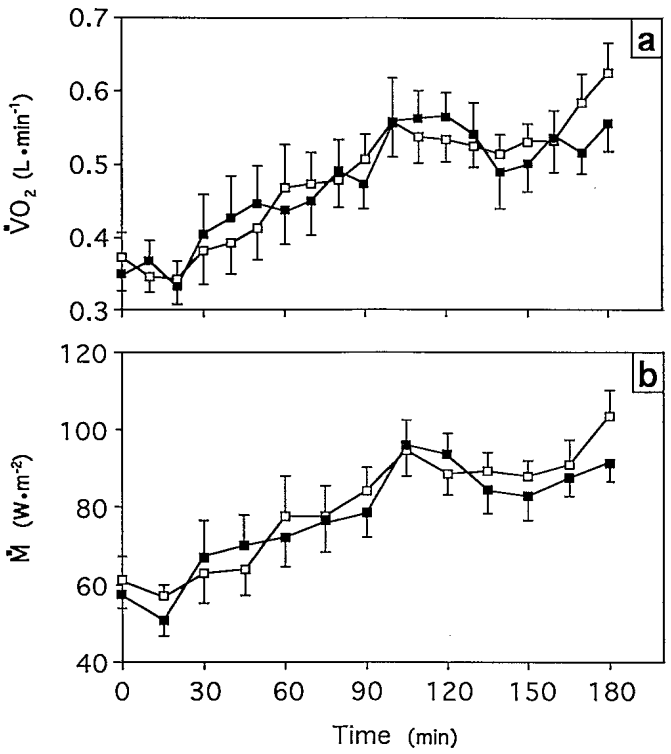

Fig. 3. a) Rates of oxygen consumption [$\dot{V}o_2$, (STPD)] and b) metabolic heat production ($\dot{M}$) in both conditions: placebo (□) and modafinil (■) during the cold-exposure tests. Each point is the average of 10 min for the nine subjects (±SEM). There is no statistical difference between conditions.

that dantrolene sodium, a specific inhibitor of calcium release from sarcoplasmic reticulum of muscle cells, could be a potent inhibitor of the hyperthermia induced in normal subjects by amphetamine derivatives (15) reinforces this hypothesis. Moreover, in the central nervous system it seems likely that amphetamines act presynaptically on catecholaminergic nerve terminals, whereas modafinil acts as a central a1-agonist on the noradrenergic system (9) and has not yet been reported to have any major peripheral action (10). These different actions might explain the different thermal effects of these drugs.

During sleep deprivation, the ability to thermoregulate during cold exposure does not seem to be impaired (3,7). However in thermoneutral resting conditions, T_{re} is generally lower in sleep-deprived subjects than in control subjects (according to the circadian variations of T_{re}; 2,3). In these conditions, modafinil could be detrimental by decreasing the metabolic heat production.

In summary, the present results demonstrate that modafinil does not produce any hyperthermia at rest at thermal neutrality, nor does it significantly affect cold tolerance under normal conditions. However, a tendency for a greater heat debt during a standardized cold-exposure test after ingesting modafinil is suggested, through a slight decrease in metabolic heat production and a slight increase in heat loss. Further studies are needed to determine if this tendency might be magnified under the sleep-deprivation of SUSOP's, during which military personnel would most likely use modafinil.

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