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Characteristics of norepinephrine stimulated thermogenesis in undernourished subjects

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Abstract. Thermoregulatory thermogenesis was evaluated in chronically undernourished subjects as well as normally nourished controls by 60 min infusions of norepinephrine at a calculated dose of 0·15 μg/kg fat free mass/min. There was a significant (P<0·05) reduction in the thermogenic response to norepinephrine in the undernourished labourers. When the characteristics of response were evaluated, the baseline and peak responses were comparable in both groups. However, the steepness of the response was greater (P<0·05) in the undernourished subjects. The time to register a threshold response of 5 ml per min increase in oxygen consumption over the baseline after the start of infusion was longer in undernourished (about 20 min) as compared to the controls (about 10 min). It appears that, while the undernourished subjects have a reduced thermogenic component in their energy output, their peak capacity or potential for regulatory thermogenesis is the same as that in control subjects, since their thermogenic response has a greater slope. It is possible that chronically undernourished subjects may have a suppressed response over shorter periods of stimulation (less than 20 min), that is, before steady state thermogenic responses are achieved.

Keywords. Thermogenesis; norepinephrine; undernutrition; response characteristics.

1. Introduction

Reduction in regulatory thermogenesis in chronically undernourished individuals has been described as a probable mechanism of conserving energy (Kurpad *et al* 1989a, b). Since regulatory thermogenesis is controlled by the sympathetic nervous system (SNS) through the release of catecholamines (Landsberg and Young 1984; Rothwell and Stock 1984), this component of energy expenditure has been estimated using a constant infusion or infusions of norepinephrine (NE) with assessment of the peak or average increase in oxygen consumption (V_{O_2}) as the response during the stimulus. With the assumption that the biological response is proportional to hormone concentration, it is possible to study this thermogenic response in terms of a dynamic model, in order to uncover its mechanisms. Since it is possible to study the kinetics of hormone receptor interactions indirectly, by measuring the biological responses of these hormones on their target cells (Moyle *et al* 1978), the data from an infusion experiment can be fitted to a logistic equation, and the parameters which define the characteristics of the response can be analysed. This study was therefore designed to assess differences in the pattern of thermogenesis between

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Abbreviations used: SNS, Sympathetic nervons system; NE, norepinephrine; V_{O_2} volume of oxygen consumed in ml/min; MJ, megajoules; BMI, body mass indices; RQ, respiratory quotient; FFM, fat free mass; MSSD, mean square successive difference; FFA, free fatty acid.

chronically undernourished individuals and well nourished controls. The patterns of response were categorized and their characteristics analysed using a four parameter logistic equation (Rodbard and Frazier 1975).

2. Methods

2.1 *Subject selection*

Thirty-three healthy adult male volunteers aged between 19 and 28 years were investigated. Twenty-one of these (controls) were medical students from the upper socio-economic strata who had daily patterns of physical activity indicative of a sedentary to moderately active life with access to adequate dietary intakes that provided energy intakes (by 24 h dietary recall) of 10 megajoules (MJ) per day. The remaining subjects were chronically undernourished labourers who were from a lower socio-economic group and led a physically active life which involved physical labour several days in a week. Their habitual daily energy intakes were about 8 MJ per day. The chronically undernourished subjects were anthropometrically smaller than the controls, probably the result of long term energy inadequacy since childhood. The control subjects were subdivided into two groups such that one group had body mass indices (BMI, weight/height^2) of <18·5 kg/m^2 and which were similar to the undernourished subjects. This group of lean subjects (n = 10) is called 'underweight controls' and the remaining subjects are called 'normal weight' controls (BMI 20, n=11, table 1).

Table 1. Anthropometric indices and dietary intakes.

Group	Height (cm)	Weight (kg)	BMI	Fat (%)	FFM (kg)	Energy (kJ/day)	Protein (g/day)
NW (n=11)	175·29 ± 6·51	63·72 ± 5·32	20·64 ± 0·7	15·48 ± 3·8	53·78 ± 4·74	11268·59 ± 1429·47	77·3 ± 19·92
UW (n=10)	172·62 ± 7·82	50·06† ± 4·59	16·9† ± 1·26	9·54† ± 1·66	45·21† ± 4·5	9922·91 ± 1575·92	62·6 ± 15·44
UN (n=12)	162·91 +*** ± 6·14	45·97*** ± 4·58	17·3*** ± 1·1	8·7*** ± 1·31	42·01 +*** ± 4·56	7856·17 ++*** ± 607·12	40·47 ++*** ± 6·49

Values are means ±SD in normal weight (NW), underweight (UW) and undernourished (UN) groups; n, no. of subjects. ***, P<0·001, UN *vs* NW; +, ++, P<0·05, P<0·01, UN *vs* UW; †, ††, P<0·05, P < 0·01, NW *vs* UW; BMI, Body mass index; FFM, fat free mass.

2.2 *Experimental protocol*

All subjects reported to the laboratory in the morning after a 12 h fast. The experimental protocol consisted of intravenous cannulation of the arm using a 20G IV Intracath (Critikon Inc., USA) and connecting tubes. This was kept patent using sterile 3·8% sodium citrate solution. The intracath was used for infusion of NE by

connecting it to a variable rate infusion pump (Sage Instruments, USA) which was previously calibrated. The subject was given a 1 h period of rest after which a ventilated hood system was used to monitor oxygen consumption. This consisted of a sealed hood around the subject's head, which was ventilated at 50 L of fresh air per min. Incoming and outgoing air were analysed using a Servomex paramagnetic O_2 analyser (Sybron Taylor, UK), an infrared CO_2 analyser (ADC Instruments, UK), and a dew point hygrometer (General Electric, USA) for humidity. The analysers were calibrated using standard calibration gases (Indian Oxygen Ltd., Bombay). These variables, along with ambient temperature, were fed into a Solartron urinate scanner interfaced with a computer for online analysis (Shetty *et al* 1987). Minute to minute O_2, CO_2 and respiratory quotient (RQ) were thus obtained for each subject. After measurement of basal O_2 consumption for 30 min continuously, NE was infused as a single dose for 60 min. The dose was standardized for all individuals at 0·15 μg/kg fat free mass/min; fat free mass (FFM) being derived from fat mass (FM) which was estimated from sum of four skinfolds, *i.e.* biceps, triceps, subscapular and supra-iliac, using age and gender specific predictive equations (Durnin and Womersley 1974). The subjects were instructed to remain absolutely still during the infusion. Oxygen consumption was averaged for 5 min intervals and the response to NE was followed using running means of these data points. The peak response was thus the highest running mean observed during the steady state.

The subjects' responses were classified into two groups: (i) responders (those with a NE stimulated peak O_2 increment of > 5% over the baseline and (ii) non-responders or minimal responders, whose O_2 consumption did not exceed 5% over the baseline. On inspection, the responders could be further sub divided into 2 groups: (i) those whose response started early (5–10 min after the start of the infusion), and (ii) those whose response started late (15–20 min after the start of the infusion). The start of the response was taken to be the first point of time when the O_2 consumption increased to more than 3% over basal consumption, after the start of the NE infusion. This value of 3% was chosen since baseline V_{O_2} is known to fluctuate to within ± 3% (Soares *et al* 1989).

2.3 *Calculations and predictions*

For the purpose of evaluating the kinetics of the response, a four parameter logistic equation was chosen for curve fitting (DeLean and Rodbard 1979; Rodbard and Frazier 1975):

$$y = [(a - d)/(1 + (x/c)^b)] + d,$$

where the maximum and minimum responses are the terms d and a respectively, the 50% intercept or ED_{50} (concentration of hormone at half maximal response) is the term c, and the slope of the curve of the 'steepness factor' (which is analogous, but not similar, to the Hill co-efficient) is the term b (Rodbard 1974; Moyle *et al* 1978). The measured responses were plotted on the ordinate, and time was plotted instead of hormone concentration on the abscissa. The latter was based on the assumption that hormone concentration in the blood increases exponentially with time during a constant rate infusion of the hormone (Gurpide 1971). In this context therefore, the term c would imply the time taken to reach the half maximal response. The

response curves were fitted to the equation using non-linear interactive curve fitting procedures using the least squares technique (Bard 1974).

Statistical analysis of all data including anthropometric indices was based on the unpaired Student's *t* test.

Ethical approval was obtained for the study from a duly constituted human investigation committee of the medical school and all subjects gave fully informed written consent.

3. Results

The chronically undernourished subjects were significantly shorter and had lower body weights than the controls. However their FFM's were comparable to those of the underweight controls (table 1). Table 2 gives the observed thermogenic response

Table 2. Changes in O_2 consumption and RQ following NE stimulation.

	Resting metabolic rate		Increase in O_2 consumption		Respiratory quotient		
Group	ml/min	ml/kg FFM/min	ml/min	ml/kg FFM/min	Basal	Peak	Nadir
NW ($n=11$)	213·18 ± 28·0	3·99 ± 0·36	25·37 ± 13·39	0·48 ± 0·26	0·85 ± 0·06	0·95 ± 0·08	0·76 ± 0·06
UW ($n=10$)	185·11† ± 19·9	4·1 ± 0·3	16·65 ± 5·31	0·36 ± 0·1	0·82 ± 0·06	0·91 ± 0·06	0·78 ± 0·05
UN ($n=12$)	177·29** ± 25·54	4·22 ± 0·38	10·25++** ± 4·31	0·24++** ± 0·09	0·95++** ± 0·1	1·04++* ± 0·1	0·89++** ± 0·08

Values are means ±SD. See table 1 for abbreviations used; *n*, no. of subjects.
*, **, ***, P <0·05, 0·01, 0·001, UN *vs* NW; + +, P <0·01, UN *vs* UW; †P < 0·05, NW *vs* UW.

to NE in all groups of subjects. The basal or resting O_2 consumption was comparable in both the anthropometrically similar groups. When the responses from all infusions were used, the increment in the O_2 consumption in response to NE stimulation (average NE stimulated O_2 consumption – basal O_2 consumption), standardized for FFM, was significantly lower in the undernourished as compared to all controls (P < 0·001). However, inspection of the peak responses (of the responders) in both groups showed no significant differences, especially when expressed per kg FFM (table 3). When the pattern of the O_2 consumption curves was analysed, it was found that in the underweight control subjects, 9 subjects had responses in the 'early responder' category while one was a late responder. The normal weight controls had 8 'early responders' while 3 were 'late responders'. Taken together, the entire control group had 17 'early responders'; and 4 ''ate responders'. None of the control subjects were in the 'non responders' category. In the undernourished group, 2 subjects were 'early responders' and 6 were 'late responders'. The remaining 4 subjects were 'non responders'. The predominant pattern therefore was of an early response in the controls, and a late or minimal response in the undernourished. The average lag time of the response (mean SD).

Table 3. Observed and estimated parameters of responses.

Group	Maximal response d (ml/min) Observed	Maximal response d (ml/min) Estimated	Basal response a (ml/min) Observed	Basal response a (ml/min) Estimated	Time for 1/2 max. response c (min) Observed	Time for 1/2 max. response c (min) Estimated	Steepness factor b	Maximal response (ml/kg FFM/min)	Lag time (l) (min)
NW+UW	234·09	240·18	199·9	201·73	23·17	26·55	2·65	4·69	8·23
($n=15$)	±	±	±	±	±	±	±	±	±
	36·24	39·17	27·87	28·12	7·35	9·29	1·33	0·53	5·24
NW	256·17	263·96	212·76	214·8	23·38	27·48	2·59	4·88	8·81
($n=8$)	±	±	±	±	±	±	±	±	±
	28·32	32·40	25·46	26·19	6·71	6·75	1·28	0·59	5·63
UW	208·86†	213·00†	185·2	186·80	22·93	25·53	2·72	4·59	7·57
($n=7$)	±	±	±	±	±	±	±	±	±
	27·12	27·20	25·15	23·60	8·57	12·05	1·49	0·33	5·13
UN	207·11**○○	205·25**○○	183·98*	184·77*	26·25	24·96	7·56+*	4·8	21·25++○○
($n=6$)	±	±	±	±	±	±	±	±	±
	29·69	29·01	21·61	24·98	9·45	11·46	5·03	0·26	9·72

Values are means ± SD. See text and table 1 for abbreviations used.
First group comprises the NW and UW control subjects taken together; n, no. of subjects.
○○, $P<0·01$, UN *vs* (NW+UW); *, **, $P<0·05, 0·01$, UN *vs* NW; +, ++, $P<0·5, 0·01$, UN *vs* UW; †$P<0·05$, NW *vs* UW.

in the underweight and normal weight controls was 7·57± 5·13 and 8·81 ± 5·63 min respectively, while it was 21·25 ± 9·72 min ($P<0·01$) in the undernourished.

When the data from the 'responders' in all groups was subjected to analysis by the 4 parameter equation, it was found that 2 subjects from the underweight controls, 1 subject from the normal weight controls and 1 subject from the undernourished had responses that did not fit the equation, either because they had not achieved a steady state, or because the data was noisy; these four subjects were removed from the data base. In the remaining subjects, there was a close agreement between the calculated and observed parameters *d, a* and *c*. The residuals were tested using the runs test and the mean square successive difference (MSSD) test, In all except five subjects, the observed number of sign runs was within the expected range ($P< 0·05$), and the MSSD was good. In the remaining five subjects in whom the runs and MSSD test showed slight departures from random behaviour, the data was reanalysed after removing those values whose residuals lay outside 1 SD from the mean residual, and good fits were obtained. The predominant value of '*b*', the steepness factor, was high (about 7) in the undernourished and low (about 2·5) in the controls. On this basis, we analysed the mean responses of the different groups using two qualifying factors for each group. These were the lag time and the value of '*b*', for which the cut off value was set at the mean value of the factor ± 1 SD. On this basis, there remained 6 undernourished responders, 7 underweight control responders and 8 normal weight control responders. The mean values of these subjects' parameters are presented in table 3. Representative data and the fitted lines are shown in figure 1 for each group.

The mean RQ of the undernourished subjects was higher at rest as well as during the infusion, when compared to the controls (table 2). The response to NE infusions in all subjects was biphasic, with an initially high level falling towards the end of the infusion to a lower level. The extent of this drop was higher in the controls, while in the undernourished subjects, the RQ remained closer to 1·0. The switch in RQ occurred at about 10 min, and did not correspond to the 'lag time'.

4. Discussion

The present study demonstrates that there is a suppressed thermogenic response to NE in undernourished labourers, as shown by the average increments over the stimulation period. This suppression persists even when the response is corrected for FFM differences. Such changes in the regulatory thermogenic component of energy output are being recognized as important adaptive responses in states of altered nutrition in humans, such as obesity (Jécquier 1984). These studies have looked at either the average increment over basal expressed as a percentage (Welle 1985; Katzeff *et al* 1986; Kush *et al* 1986); or as a peak response (Sjostrom *et al* 1983; Jung *et al* 1979). There are also reports on the heterogeneity of the thermogenic response (Connacher *et al* 1988), as well as in autonomic function (Peterson *et al* 1988) in obese subjects. It is also observed (this study) that the response of individuals to NE could be quick or slow. This would give rise to different average responses when the area under the curve is evaluated, but not when peak responses are compared. The physiological basis for such a classification is given below. A heterogeneous response pattern also existed in the present study; however, there remained a predominant pattern of response in each group. When

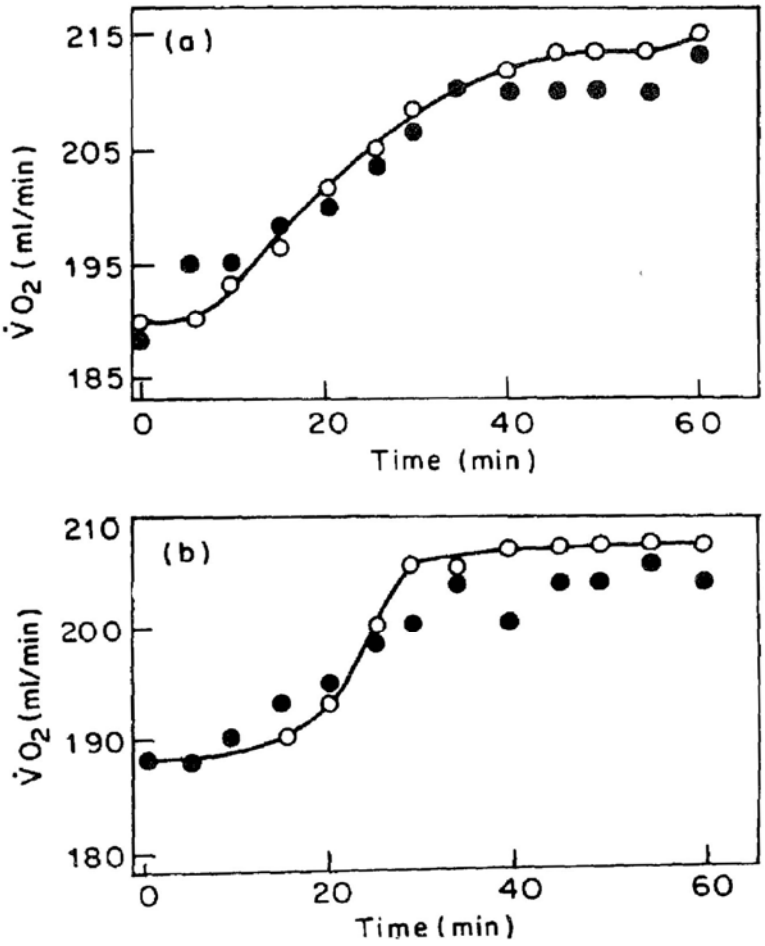

Figure 1. Observed (●) and estimated (O) V_{O_2} values at rest and during the NE infusion in a typical **(a)** control 'responder' and **(b)** undernourished 'responder'.

the average increments of the groups are taken into consideration, it is evident that there are differences between the groups. However, these differences tend to become less clear when only 'responders' are assessed from all groups. Then, the average increment over basal, per kg FFM, was 0·499 ± 0·22, 0·351 ± 0·083 and 0·295 ± 0·083 (P <0·05 for normal weight control *vs* undernourished) in the normal weight controls (n = 8), underweight controls (n = 7) and undernourished (n = 6) respectively, even though the pattern of response was still distinct between the groups. In this context, when average or integrated values for the response appear to be comparable between the groups, the pattern of response may be an important difference that may have to be considered.

It is also well recognized that this regulatory component of thermogenesis is modulated by the sympathetic nervous system and mediated through the release and actions of catecholamines such as NE which are thermogenic (Rothwell and Stock

1984). It is hence proper to examine the interrelationships between these hormones and their receptors as well as their physiological responses. Models for assessing hormone receptor interactions have been based on the functional responses induced by testosterone on Leydig cells (Moyle *et al* 1978). This has been called functional hormone binding, and is potentially applicable to any biological system in which ligand binding is followed by a measurable response. The response is proportional to the concentration of free hormone, which in turn determines the fraction of receptors occupied at steady state. The present model used for prediction of parameters in this experiment is a general one, less specific than other explicit mechanistic models (Monod *et al* 1965; Koshland *et al* 1986). This had been found useful in describing dose-response curves for responses stimulated by hormones *in vitro* (Catt *et al* 1972; Sayers *et al* 1972). We found a good comparison between atleast three predicted and observed parameters in the present equation which indicated its usefulness in the prediction of some characteristics of the thermogenic response *in vivo.* Examination of data shows that the parameters *a* and *d,* which are the minimal and maximal responses respectively were comparable in both groups though slightly lower in the undernourished. The factor "*b*", which is the slope of the curve, is indicative of the steepness of the response. In this experiment, the undernourished labourers had an estimated value of $b=7{\cdot}7$ as compared to the controls, whose value of *b* was equal to 2·5. Yet, the average increment in response to NE was lower in the undernourished subjects. This apparent discrepancy can be explained by the threshold time of response in the same group. The average time to register an increase of 3% in O_2 consumption over the baseline was about 15-20 min after the start of the infusion in the undernourished subjects as compared to about 10 min in the controls (see figure 1). Since the parameters *a* and *d* were comparable in both groups of subjects and the half time of response was about 20–25 min, it is evident that 'the slope of the response curve in the undernourished labourers would be steep'. Mechanisms like enzyme cascades, substrate mobilization, co-operativity and receptor numbers are possible explanations for this phenomenon.

The RQ's of the undernourished subjects showed a consistently higher value than that of the controls. The RQ response to an infusion of NE is biphasic, increasing in the first 10 min, and then dropping to a low 'fat oxidation' level towards the end of the infusion. While this pattern was seen in all groups, the lowest RQ recorded in the undernourished subjects was significantly higher than the corresponding RQ in the controls. Taken together with the higher basal RQ, it is possible that, given smaller fat stores, the undernourished preferentially utilize carbohydrate under conditions of stress. However, the underweight controls had similar fat stores and it is likely that other factors like energy intake, SNS adaptation also contribute to the response. Earlier studies have also demonstrated higher resting RQ's for undernourished subjects (Shetty 1984). Using resting protein oxidation data generated for Indian subjects in this laboratory (in similar groups) from urinary nitrogen using 2 h urine collections, where the values were 2·41 g/h in the undernourished and underweight controls and 2·88 g/h in the normal weight controls (Piers *et al* 1992), and assuming that no changes in protein oxidation occurred with short term NE stimulation, it was found that substrate mobilization rates (Frayn 1983) after 30 min of NE infusion were 11·59 and 2·49 g/h of carbohydrate and fat respectively in the normal weight controls, 9·57 and 2·28 g/h

in the underweight controls, and 14·09 and 0·25 g/h in the undernourished subjects. The corresponding values for the second 30 min of the infusion were 4·9 and 5·5 g/h, 6·46 and 3·74 g/h, and 10·75 and 1·71 g/h in the same order. The mobilization of fat following NE infusion is therefore highest in the normal weight controls, less in the underweight controls and least in the undernourished. This agrees with the body fat estimates in these groups. The high RQ's in the first phase of the response may be related to the effect of catecholamines on the carotid body (Lloyd and Cunningham 1963) or on the central nervous system (Folgering 1980) causing increased ventilation (Joy 1963; Whelan and Young 1953) and hence an apparent increase in CO_2 production. However, CO_2 measurements in subjects receiving adrenaline infusion showed that ventilatory changes did not explain changes in the RQ (Sjostrom *et al* 1983). The decreasing carbohydrate oxidation and increasing fat oxidation seen in the later part of the infusion could be due to free fatty acid (FFA) induced suppression of glucose uptake (Randle *et al* 1964), as also to an increase in FFA oxidation (Issekutz *et al* 1968).

In conclusion, the thermogenic response to NE appears to be heterogeneous in groups of individuals. Undernourished subjects have a decrease in the thermogenic component of their energy expenditure; however, an analysis of their responses shows that while the undernourished subjects predominantly respond late or not at all, there seems to be a steep response factor which operates after their response thresholds are reached. This allows for almost comparable peak values to be reached, such that peak capacity for thermogenesis remains unaltered although over the entire duration of the infusion the average O_2 consumption was significantly less and the preferential substrate for oxidation was carbohydrate in the undernourished. It is evident that the four parameter logistic equation can be used to evaluate such differences. However, its use may be restricted to those subjects in whom a clear cut response is obtained. We have also reported (Kurpad *et al* 1989c) that repeated infusions of the same dose of NE results in potentiation of the average thermogenic response. The patterns of thermogenic response to NE infusion indicate that the suppression in chronically undernourished individuals may be in part related to the latency of the response, while théir ability to attain a peak response comparable to the well nourished is not compromised.

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