suppressed at lower [NA] than phase 2, implying a differential sensitivity of the 2 phases to NA inhibition.

This is examined further in figure B, which presents insulin outputs as a function of [NA]. Basal secretion is represented by output at 20 min, phase 1 by output at 40 min, and phase 2 by output at 60 min. In all cases there is highly significant correlation between [NA] and ln-transformed output (basal, $r = -0.858$; phase 1, $r = -0.970$; phase 2 $r = -0.916$: p always < 0.001). 2-way analysis of variance of the data in figure B shows a significant output vs time interaction term (F_s [10, 90] = 12.64, $p < 0.001$), indicating significant differences in the slopes of the 3 lines. Significant 2-way interactions are also demonstrated in paired comparisons of the responses: basal vs phase 1, F_s [5,60] = 16.23; basal vs phase 2, F_s [5, 60] = 12.24; phase 1 vs phase 2, F_s [5,60] = 70.35: p always < 0.001. The slopes of the regression lines calculated upon ln-transformed insulin outputs are basal = 1.013, phase 1 = 1.017, phase 2 = 1.019. Sensitivities of the 3 components of the secretion profile to NA inhibition are thus basal < phase 1 < phase 2.

These findings are consistent with earlier in vivo studies upon the effects of NA and alpha-adrenergic blockers on insulin secretion. Endogenous NA has a greater effect upon glucose-induced than basal secretion[12], and in patients with phaeochromocytoma, basal insulin secretion is frequently unaltered, while glucose-induced secretion is substantially reduced[19]. With administration of exogenous alpha-adrenergic agonists, greater inhibition of glucose-induced than basal insulin secretion has been reported[2], supporting the present findings. With alpha-adrenergic blockade in vivo, basal secretion is unaltered, while glucose-induced secretion is markedly enhanced[20,21]. Also, in the human subject, noradrenaline infusion reduces basal insulin secretion by some 50%, while abolishing glucose-induced secretion[22]. The present data therefore provide in vitro evidence for differential sensitivities of basal and glucose-induced phases of insulin secretion to adrenergic inhibition.

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Age-related adrenocortical response to short-term starvation in young rats

M.A. Ventura[1]

Unité de Neuropharmacologie - Université de Paris XI, F-91405 Orsay Cedex (France), 25 September 1981

Summary. In a study of the response to short-term starvation in 4-week-old and 7-week-old male rats, it was found that in the younger rats corticosterone levels rose earlier and reached higher levels; they fell after refeeding to a greater extent. Body weight loss followed the same pattern. Younger rats seem to adapt better to fasting and refeeding.

Food deprivation exerts a stimulatory effect on adrenocortical activity[2-6]. Corticosterone levels increase in response to fasting, a) as a result of emotional distress, and b) as a component of the physiological adaptation to lack of food[7]. This hormone plays an important role in the metabolic response to fasting conditions, i.e., in gluconeogenesis[8]. Furthermore, the loss in body weight has been found to correlate with corticosterone levels[3,8]. In this paper, we have compared the effect of short-term starvation, as well as refeeding, on corticosterone levels and body weight in young males of 2 different ages: Post-weaning (4 weeks) and young adult (7 weeks) rats. The effect of chronic underfeeding is also reported.

Male Sherman rats were used, reared in the laboratory under natural light/dark conditions, constant temperature (22 ± 1 °C) and commercial food and tap water 'ad libitum' until the beginning of the experiments, carried out in autumn and winter. The composition of the food, (Extralabo No. 25 biscuits) was as follows: water: 8.2%, fat: 5.6%, minerals: 8.2%, nitrogenous substances: 25%, cellulose: 3.8%, nonnitrogenous extractive: 49.6%. In short-term experiments, 4 weeks (60 ± 10 g) and 7 weeks (141 ± 8 g) old rats were subjected to the following conditions: a) Control-food 'ad libitum' (F), b) 24 h of starvation (S), c) 60 h of starvation, d) 60 h of starvation plus 24 h of food 'ad libitum'. In long-term experiments, 2 groups of 4-week-old rats were nourished for 3 weeks as follows: a): Control = food 'ad libitum', b) 5 g/day of food, given at 09.00 h. The rats were decapitated at the end of the last/fasting period, between 09.00 h and 11.00 h in all cases. Corticosterone assay was carried out in plasma and adrenal homogenates according to the fluorometric method of De Moor[9].

Effect of starvation on adrenal corticosterone levels of 4- and 7-week-old rats (W)

	Weeks	Control	24 h starvation	60 h starvation	60 h starvation + 24 h food	5 g/day
µg/gland × 10	4	2.2 ± 0.36 1	47.4 ± 5.5 3	69.0 ± 10.4 5	14.0 ± 2.5 7	-
	7	10.7 ± 3.0 2	20.1 ± 6.3 4	31.7 ± 9.0 6	27.9 ± 4.0 8	59.7 ± 4.2
µg/mg Pr × 10	4	1.6 ± 0.24 1	21.7 ± 3.0 3	32.9 ± 5.7 5	7.2 ± 1.3 7	-
	7	2.9 ± 0.77 2	6.7 ± 2.1 4	12.3 ± 3.4 6	6.2 ± 1.13 8	17.0 ± 1.7

Mean ± SEM, n = 10 except 5 g/day: n = 9. The groups are numbered 1 to 8, to identify them in the statistical analysis (SNK-test) (see legend of fig. 1). 5 g/day: 5 g of food per day, for 3 weeks, at 09.00 h.
ANOVA: µg/gland: overall, starvation factor and interaction, $p < 0.001$; age factor, n.s. µg/mg protein: overall, starvation and age factors and interaction, $p < 0.001$.

SNK-test: µg/gland 1 2 7 4 6 8 3 5
µg/mg protein 1 2 4 8 7 6 3 5

Adrenal proteins were determined by the Lowry method[10]. The step-wise statistical analysis included: a) basic computations ($\bar{x}$, s^2, SEM, etc.), b) F-max test for homogeneity of variances, c) log-transformation if required, d) 2-way analysis of variance (ANOVA) model I, with equal sample size, e) Student-Neumann-Keuls (SNK) a posteriori test ($\alpha = 0.05$). Statistical procedures were taken from Sokal and Rohlf[11].

Control 4-week-old rats showed lower basal corticosterone values than control 7-week-old rats, both in plasma (fig. 1) and adrenal, when expressed per total gland (table), or per g adrenal wet weight (results not shown). This difference was no longer significant when the results were expressed in µg/mg of protein. The increase in corticosterone levels in response to starvation (fig. 1 and table) was earlier and higher, and the fall after refeeding more pronounced, in younger than in older rats. This was observed for plasma as well as adrenal levels. The changes in body weight (fig. 2), expressed in absolute values (in g) or percentage of initial body weight, closely paralleled the variations in corticosterone levels; weight loss, as well as recovery, occurred earlier in 4-week-old rats. After 3 weeks of food restriction to 5 g/day, corticosterone levels in plasma (39.2 ± 4.5 µg/100 ml) and adrenal (table) were 6 times higher than those observed age-paired animals fed 'ad libitum' (controls). Body weight was just maintained under these feeding conditions; −6% change over the 3-week period, vs 109 ± 8% in controls.

In adult rats subjected to progressive starvation, plasma corticosterone levels increase in a time-dependent way. The normal levels observed after 24 h rise significantly by the end of the 2nd day, and persist for at least 1 week[5,6]. 1 week of refeeding restores basal levels[6]. In 1-month-old rats, significant increases in corticosterone levels have been reported after 24 h of fasting[4]; 50-day-old, but not 90-day-old male rats responded to a 24-h fast by an increase in corticosterone levels[12]. Our results for short-term starvation are in good agreement with the above mentioned data. Moreover, clear differences between 4- and 7-week-old rats have been observed, for corticosterone levels as well as body weight; the response of younger rats to fasting was earlier and more marked, and the recovery after refeeding easier. In addition, chronic food restriction brought about a 6-fold increase in corticosterone levels in young rats, whereas in adult rats Usher et al.[13] found the levels to be only double. Starvation by itself does not modify the circadian pattern, until the increasing hormone levels fade it[6]. On the other hand, restricted access to food shifts the

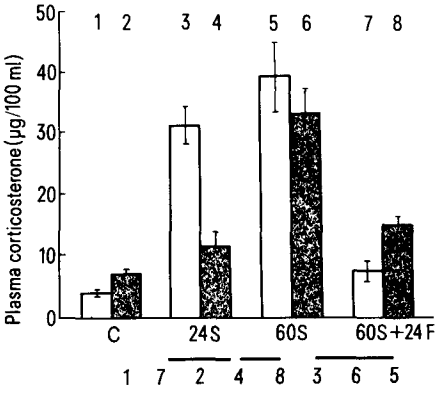

Figure 1. Effect of starvation on plasma corticosterone levels of 4-week-old (open columns) and 7-week-old (dashed columns) male rats (mean ± SEM, N = 10). 1, 2: Control (C): food (F) ad libitum; 3, 4: 24 h starvation (S); 5, 6: 60 h starvation; 7, 8: 60 h starvation + 24 h food ad libitum.
Statistical analysis: ANOVA: overall, starvation factor and interaction, $p < 0.001$. Age factor, n.s. SNK test: see bottom of the figure. The means are arrayed in increasing order of magnitude (from left to right) and the lines represent the sets of means where no difference was found ($\alpha = 0.05$).

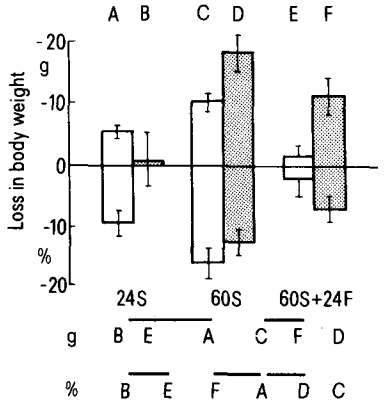

Figure 2. Effect of starvation on body weight of 4-week-old (open columns) and 7-week-old (dashed columns) male rats. Upper panel: Absolute loss, in g; lower panel: relative loss, in percentage of the initial body weight (%). A, B: 24 h starvation; C, D: 60 h starvation; E, F: 60 h starvation + 24 h food ad libitum.
Statistical analysis: ANOVA: a) g: overall and starvation factor, $p < 0.001$. Age factor, n.s. Interaction, $p < 0.025$. b) %: overall and age factor, $p < 0.001$. Starvation factor, $p < 0.005$. Interaction, $p < 0.01$. SNK-test: see figure 1 for explanation.

rhythm, so that the peak appears just before food presentation[6]. This shift could explain the high morning levels observed in the group fed 5 g/day at 09.00 h (i.e., time and quantity restricted). However, age-paired animals, fed ad libitum from 09.00 to 17.00 h (that is, time, but not quantity restricted) showed significantly lower hormone levels ($\alpha < 0.05$)[14]. Thus, the difference observed can, in all likelihood, be related to the limited food intake.

A more efficient adaptation of younger rats to fasting and refeeding has been reported for other physiological parameters, e.g. protein turn-over. Starvation decreases hepatic RNA and protein, early, at any age, but muscular and cardiac protein and RNA loss occurs to a greater extent in younger rats[15]. In fact, protein content decreases because of diminished synthesis, as well as increased catabolism[16]. The subsequent increase in amino acid availability fits well with the present data, concerning higher corticosterone levels in younger rats, because of the well known role of this hormone in gluconeogenesis[8]. After refeeding, the incorporation of ^{14}C-leucine into protein recovers more efficiently using ribosomes from younger animals[16]. As a matter of fact, corticosterone plays an essential role in the 'enzyme overshoot' observed in the refed rats[17], related to the increased efficiency of food utilization after weight loss[18].

The high corticosterone levels observed under fasting conditions have been ascribed to a diminished rate of disappearence of the hormone without changes in the secretion rate[19]. The latter possibility has been partly overcome by the observation of changes in CRF and ACTH levels in starving rats[5]. Such an activation of the pituitary-adrenal axis could be related to serotonergic mechanisms: brain serotonin (5-HT) turnover was reported to increase under fasting conditions[20]. It should be recalled that a stimulatory role has been claimed for 5-HT in the control of the adrenocortical function[21]. The higher levels of corticosterone found in younger rats could be related to immature feed-back mechanisms; according to Goldman et al.[22], the control of the acute activation of the pituitary-adrenal system is fully mature in weanling rats, but the negative feedback mechanism continues to increase in effectiveness between weaning age and adulthood.

1 Present address: Pharmacologie Biochimique, CHU Cochin, 24, rue du Fb StJacques, F-75014 Paris (France).
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DISPUTANDUM

Tissue channels, prelymphatics and lymphatics

Introduction

by M. Földi

D-7821 Feldberg (Federal Republic of Germany)

In a paper entitled 'Lymphatic drainage of the brain', published in 1968 with my associates in this journal (Földi, 1968), we expressed the view that - in spite of the fact that there are no lymph vessels in the brain substance - the cervical lymphatic tissue plays a role of paramount importance in the drainage of cerebral interstitial fluid. The 'perivascular spaces', described by His in 1865, have been shown to be long 'prelymphatic tissue channels' connecting the neuropil with the cervical lymphatic system.

These studies have recently been confirmed by Cserr (1980). Obviously, a blockage of a pathway key to performing a physiological task must have pathophysiological consequences. We have described lymphostatic encephalopathy as a result of cervical lymphatic blockage. This part of our studies has yet to arouse interest amoung others and awaits confirmation.

An analogous system of short tissue channels connects blood capillaries and initial lymphatics within those tissues which possess the latter. They, evidently, play an important role in microcirculation.

The reader will find pertinent studies on these topics written by two eminent scientists, the physiologist A. Hauck and the electron microscopist J.R. Casley-Smith, and a comment by A. Silberberg, who is a chemist.

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