table 2. No disparities in labeling of iodotyrosines (MIT and DIT) were noted. While no alteration in extent of labeling of the tetraiodothyronine (T_4) was observed, a significant diminution in labeling occurred in the iodothyronine, T_3, in rats maintained on sodium acetate ($p < 0.05$). This resulted in a decrease in the T_3:T_4 ratio ($p < 0.01$) below that of the control group. The data presented in table 3 show that the fraction of ^{131}I organically bound ($p < 0.01$) and the accumulation of newly formed thyroid hormone ($p < 0.05$) was significantly reduced in rats ingesting sodium acetate when subjected to the stress of an acute iodide load.

Discussion. Dietary ingestion of sodium acetate for 3 months caused a significant reduction in body weights of male Long-Evans rats. While thyroid gland weights of sodium acetate treated rats were increased significantly above the glands of control rats, thyroid weight related to body weight was almost double that observed in control rats. Moreover, thyroidal ^{131}I uptake was also markedly increased in treated rats but the circulating T_4 levels were not significantly different from the serum T_4 levels observed in the control group. The enhancement in thyrotropic activity evidenced by the elevated serum TSH levels in rats ingesting sodium acetate was responsible for the increases in thyroid weight and thyroid uptake of radioiodine. The administration of an iodide load resulted in a reduction in the capacity to organify iodide by the sodium acetate-treated rats. Moreover, chromatographic analyses of thyroid hydrolysates of rats ingesting sodium acetate revealed a significant decrease in labeling of T_3. Since labeling of T_4 was unaffected, this finding may indicate a coupling defect in the synthesis of T_3 with consequent reduction in T_3:T_4 ratios in rats chronically ingesting sodium acetate.

The view that the iodoamino composition of thyroglobulin is directly related to the iodine content[4,5] has been challenged recently by several investigators[6,7] who have suggested that additional factors such as the conformation of the thyroglobulin molecule, availability of tyrosyl residues for iodination, appropriate positioning of iodotyrosyl residues for coupling in the formation of the thyroid hormones (T_4 and T_3), pH, temperature and other factors may be important in determining the iodothyronine distribution in thyroglobulin with consequent altered T_3:T_4 ratios. Indeed, we have recently reported that chronic ingestion of mercuric chloride caused a significant reduction in percentage of labeled T_3 in rat thyroid hydrolysates perhaps reflecting a coupling defect exerted by mercury[8].

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Adaptation of the pituitary gland to prolonged LRH stimulation

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Summary. With prolonged constant rate infusion of luteinizing hormone-releasing hormone (LRH), the LH secretion rate of the rat pituitary gland changes continuously until a steady state of relative desensitization has developed. Recovery from this state can occur independently from changes in the pituitary's LH content.

Luteinizing hormone-releasing hormone (LRH) and related agonistic substances can stimulate the pituitary gonadotrophs to release LH. Upon prolonged exposure to these substances, however, the rate of LH release decreases[1-5]. This decrease is not due to a genuine exhaustion of the pituitary LH store, but rather to progressive desensitization of the gonadotrophs for these stimulatory agents. This desensitization, possibly caused by receptor-down-regulation[6,7], however, may be accompanied by a marked depletion of the pituitary LH store[8].

In the present study, attention was payed to the relationship between LRH-induced changes in pituitary LRH-responsiveness and LH content.

Materials and methods. 8-week-old female Wistar rats were ovariectomized and used for experiments 5 weeks later. At the time they weighed 200–250 g. Prolonged stimulation of

Table 1. Analysis of data of figure 1. Integrated LH release (area under the curve; AUC(24); mean ± SEM) and the maximal plasma LH concentration (MH; ng LH-RP-1; mean ± SEM) during the 1st 24 h of a 48-h first infusion (of saline or 52 ng LRH/h and during the 24 h of a 2nd infusion of LRH at the rate of 416 ng/h. Integrated LH release (AUC(72); mean ± SEM) during the complete 72-h experimental infusion period. LH content (μg LH-RP-1; mean ± SEM) of the pituitary gland at the end of the experiment

1st infusion (material)	n	1st infusion (LH response) AUC(24)	MH	2nd infusion (LH response) AUC(24)	MH	AUC(72) (LH response)	Pituitary LH-content after experiment
Saline	7	107 ± 8^a	675 ± 129^a	656 ± 96^a	6720 ± 818^a	850 ± 105	611 ± 33
LRH	7	331 ± 28^b	2905 ± 195^b	471 ± 35^b	3968 ± 565^b	933 ± 63	601 ± 45

For each column holds p(a vs b) < 0.01. No differences in last 2 columns.

LH release by the pituitary gland was effected by constant rate infusion of LRH via a cannula inserted into the right jugular vein[3]. Blood samples were taken from a cannula inserted into the right carotid artery. All operations were performed under appropriate ether anesthesia. As the experimental design required the withdrawal of a relatively large number of blood samples, an erythrocyte suspension containing a number of erythrocytes about equivalent to 2.5 ml of blood was injected after 10 h of LRH infusion (i.e. after the withdrawal of the 15th (1st experiment) or the 11th (2nd experiment) blood sample). The suspension was prepared from blood (taken by aorta punction) of ether-anesthetized 5-week-ovariectomized (OVX) rats. Plasma LH concentrations and pituitary LH contents were measured by double antibody radioimmunoassay[9,10]. NIAMDD-rat-LH-RP-1 (a gift from the NIAMDD-NIH rat hormone distribution program) was the reference preparation, while the antibody to LH was a gift from Drs J. Dullaart and J.Th.J. Uilenbroek of the Erasmus University of Rotterdam.

The curves which represent the time-course of the plasma LH concentrations have their maximum at t=2 h. From that moment on, plasma LH concentrations decline steadily and may finally stabilize[3]. From the LH-curves the 'areas under the curve' (AUC) were calculated. The AUC from t=0 to t=th is denoted as AUC(t) and expressed in arbitrary 'area units' (AU). Under the present experimental circumstances AUC(t), or integrated LH release, is linearly proportional to the amount of LH secreted during the th period[11]. In the present study the AUC(t) and the maximal height (MH) were used as parameters for the characterization of an LH-response. Data are expressed as mean ± SEM. Differences between means were assessed by the unpaired, 2-tailed Student's t-test at a level of significance of 0.05.

Experiments. Five-week OVX rats were used in order to prevent interference of ovarian hormones with the LRH-induced LH release. Although OVX rats maintain an elevated blood LH concentration, which may introduce 'noise' in the LH secretion caused by constant rate infusion of LRH, this does not interfere with the trend of LH release typical of the present experimental approach. In the 1st experiment LRH or, in the case of the control rats, saline, was infused at first at the rate of 52 ng/h for 48 h. Then all animals were infused with LRH at the rate of 416 ng/h for 24 h.

In the 2nd experiment LRH was again first infused at the rate of 52 ng/h for 48 h. Infusion was then stopped and after 24 h resumed for another 24 h. In both experiments blood samples were taken and pituitaries were removed at times apparent from 'Results' and 'Discussion' sections.

Results. Experiment 1 (see fig. 1 and table 1) shows that after 48 h of LRH infusion at the rate of 52 ng/h the pituitary gland is only partially refractory to continuing LRH stimulation: an increase of the infusion rate to 416 ng/h caused a 2nd LH-response (1st group). This response, however, was smaller than that induced by the same infusion rate in animals in which the latter infusion was preceded by a saline infusion lasting for 48 h (2nd group). The data on the integrated LH release (AUC 72)), however, show that the animals of both groups had released equal amounts of LH during the 72-h experimental period. Moreover, at the end of this period the pituitary LH contents were the same in the 2 groups of animals. These results may suggest that LRH-induced desensitization of the gonadotrophs is relative rather than absolute.

Experiment 2 (see fig. 2 and table 2) shows that upon withdrawal of LRH, pituitary responsiveness may recover from relative desensitization: when, after 48 h of LRH infusion at the rate of 52 ng/h (1st infusion), followed by withdrawal of the releasing hormone for 24 h, LRH infusion (52 ng/h) was resumed for another 24 h (2nd infusion), LH-responses were again induced. These responses were about 0.8 times as great as those induced by the first infusion, whilst the ratio between the LH contents just prior to the infusions was about 0.9. These data suggest that in 24 h the responsiveness to LRH of the pituitary gland of the

Table 2. Analysis of data of figure 2. Pituitary LH content (μg LH-RP-1/gland; mean ± SEM) prior to a 24-h 1st and a 24-h 2nd LRH infusion at the rate of 52 ng/h. Maximal plasma LH concentration (MH; ng LH-RP-1/ml; mean ± SEM) and integrated LH release (area under the curve; AUC(24); AU mean ± SEM) of the LH-responses to the 1st and the 2nd LRH infusions

Pituitary LH content prior to LRH infusion	n		LH response (n = 8)	
			MH	AUC(24)
1524 ± 115	10	1st infusion	2293 ± 243	266 ± 30
1403 ± 101	4	2nd infusion	1740 ± 109	226 ± 87

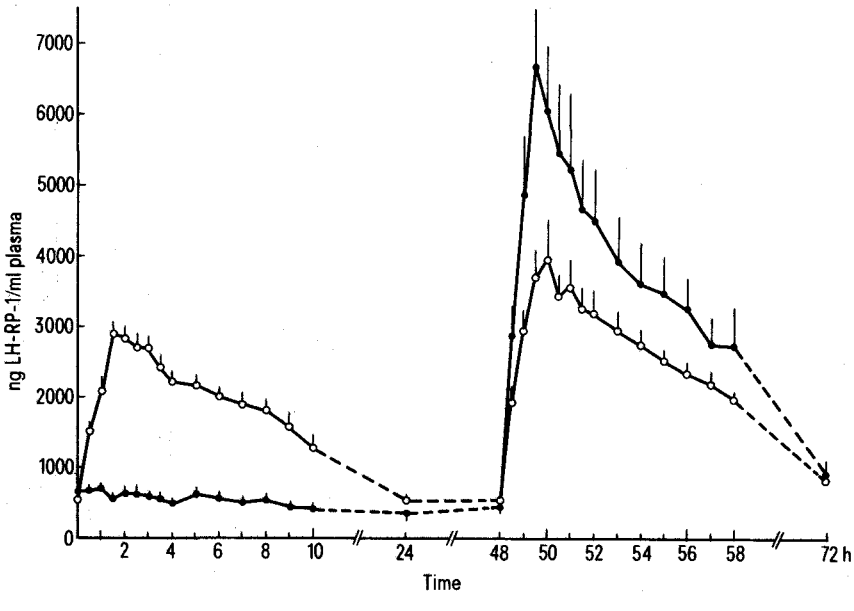

Figure 1. 1st experiment. The course of the plasma LH-concentrations (mean ± SEM) during 2 consecutive infusions the 1st lasting 48 h and the 2nd 24 h. ●——●: 1st infusion: saline; 2nd infusion: LRH (416 ng/h), (n = 7); ○——○: 1st infusion: LRH (52 ng/h); 2nd infusion: LRH (416 ng/h), (n = 7).

OVX rat can largely recover from relative desensitization, provided that exposure to LRH is discontinued and pituitary LH content is not depleted extensively.

Discussion. These experiments confirm that upon prolonged stimulation with LRH the LH secretion rate first increases and then decreases. Finally LH is secreted at a constant rate (see introduction). It is thus apparent that the pituitary gland adapts to the stimulus until it passes into a steady state. This steady state is one of relative desensitization: an increase of the LRH infusion rate could still induce an LH-response. From the magnitudes of consecutively induced LH-responses and the pituitary LH contents at the end of the experiments it can be inferred that LH-responses to staircase stimulation patterns are additive. The present experiments also suggest that changes in relative desensitization cannot solely be reduced to changes in pituitary LH content: once LRH stimulation was stopped, recovery of pituitary responsiveness to LRH occurred independently from changes in the LH stores. It is therefore apparent that the magnitude of an LRH-induced LH-response cannot be defined in terms of the absolute value of the blood LRH concentration (as established by a given LRH infusion rate[3]) and the LH content of the pituitary prior to LRH stimulation only. Apparently, also, the state of the LH release mechanism is one of the factors which determine the responsiveness of the pituitary gland to LRH, and the state of this mechanism seems to be under the control of LRH. Although definite data as to the cytological substrate of this regulatory process are lacking, this substrate may well be the LRH-receptor population of the gonadotrophs[6,7].

The induction of and recovery from relative desensitization may be physiologically relevant. In the OVX rat the elevated blood level of LH is maintained by episodic release of the hormone[12]. This is presumably due to intermittent hypothalamic LRH release[13]. Also, with intermittent LRH infusion elevated LH release is maintained rather than desensitization occurs[6]. The present observations may contribute to the explanation of this phenomenon; when intermittently exposed to LRH, the pituitary gland regularly gets the opportunity to recover from the (minor) relative desensitization caused by the previous LRH pulse. If, however, the gland is continuously exposed to LRH, relative desensitization develops and this may partly explain the well-documented antifertility effects of the releasing hormone and its highly active analogues[5,14–18].

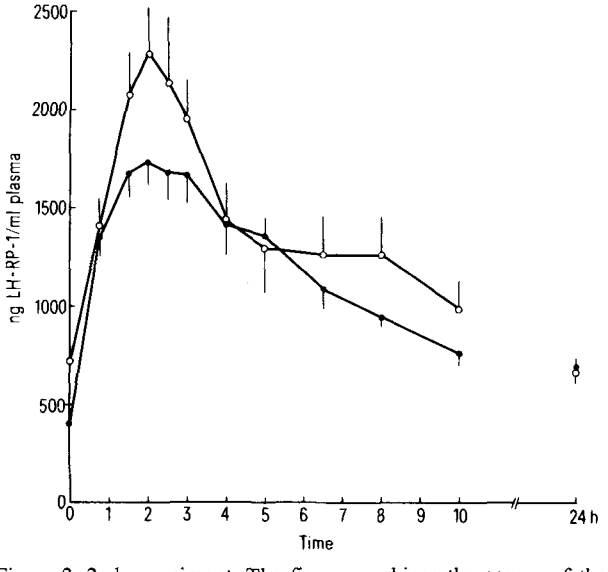

Figure 2. 2nd experiment. The figure combines the course of the plasma LH concentration (mean ± SEM) of a group of 8 rats during the 1st 24 h of a 48-h LRH infusion (52 ng/h; ○——○) and the course of the LH concentration after the end of this 48-h period, a 24-h interval and resumption of the LRH infusion for another 24 h (●——●). Only data for this latter period are included and the beginning of this period is considered t = 0 in the figure.

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Are prostaglandins involved in early estrogen action?[1]

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Summary. Prostaglandin biosynthesis inhibition by indomethacin blocks estrogen-induced uterine hyperemia, but does not block estrogen-induced uterine eosinophilia and edema.

Evidence suggesting differences in the action of estrogens in the uterus, implying multiple mechanisms of action for this hormone, has been reported[2-4]. It has been proposed that the cytosol-nuclear estrogen receptors mediate the genomic response to estrogens, i.e., increases in RNA and protein content[5]. The involvement of cyclic AMP in estro-