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].

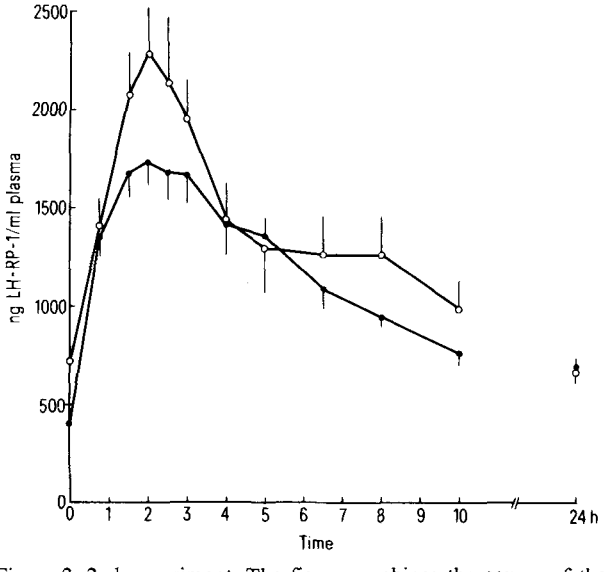

Figure 2. 2nd experiment. The figure combines the course of the plasma LH concentration (mean ± SEM) of a group of 8 rats during the 1st 24 h of a 48-h LRH infusion (52 ng/h; ○——○) and the course of the LH concentration after the end of this 48-h period, a 24-h interval and resumption of the LRH infusion 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-

Effect of indomethacin on estrogen-induced uterine eosinophilia and wet weight increase, 6 h after the administration of estradiol or vehicle to immature and adult ovariectomized rats (means ± SE)

	Control rats	Estrogen-treated rats	Estrogen-indomethacin-treated rats	Indomethacin-treated rats
Adult ovariectomized rats				
Count of eosinophils per uterine cross section	$0.05 \pm 0.03^{i,k}$	10.6 ± 2.3	13.9 ± 2.6^{g}	$0.05 \pm 0.03^{i,k}$
Uterine wet weight	115 ± 22^{jl}	235 ± 19	251 ± 31	151 ± 22^{jl}
Immature rats				
Count of eosinophils per uterine cross section	$0.01 \pm 0.01^{c,e}$	1.6 ± 0.2	1.3 ± 0.1^{a}	$0.01 \pm 0.01^{c,e}$
Uterine wet weight	$19.6 \pm 1.2^{d,f}$	33.3 ± 1.0	42.2 ± 2.2^{b}	$25.1 \pm 1.2^{d,f}$

[a,g,h] Non-significant; [b,k] $p = 0.0025$; [l] $p = 0.0125$; [e,f] $p = 0.0005$ as compared to estrogen-treated animals. [c] Non-significant; [d] $p = 0.0125$; [i,j] $p = 0.025$ as compared to indomethacin-treated animals.

gen-induced increase in uterine glycogen content has also been suggested[6]. Estrogen-induced uterine eosinophilia may be involved in some early non-genomic parameters of estrogen stimulation, such as uterine edema, increase in vascular permeability and release of histamine[7,8].

Non-specific acute inflammatory responses and the early non-genomic response to estrogens are characterized by similar processes; leukocyte diapedesis, increases in blood flow and in vascular permeability, release of histamine and edema. Inflammatory responses are mediated by prostaglandin release[9], therefore they are blocked by prostaglandin inhibitors such as cortisol[10] and indomethacin[11]. The early non-genomic response to estrogens is also blocked by cortisol[12], although a different mechanism has been proposed for its explanation[12,13]. To elucidate whether prostaglandins are involved in early estrogen action, we have investigated the effect of indomethacin in estrogen-induced uterine eosinophilia and edema.

Material and methods. 2 groups of animals were used in the present study; intact immature (50 g b.wt) and adult ovariectomized (300 g b.wt) Sprague-Dawley rats. Animals from each group were subjected to one of the following experimental conditions: a) estrogen treatment, b) indomethacin treatment, c) estrogen + indomethacin treatment, d) controls. Estradiol-17β (30 µg/100 g b.wt) and/or indomethacin (1 mg/100 g b.wt) or the vehicle were injected into the jugular vein under ether anesthesia, and the animals were killed 6 or 24 h after the injection. The right uterine horn was used for determination of its wet weight and the left one was histologically processed for the determination of the number of eosinophil leukocytes per cross section[8].

Results. The table shows that estrogen induces uterine eosinophilia and edema 6 h after its administration to intact immature, or adult ovariectomized, rats. Indomethacin does not block these responses in either the immature or the adult ovariectomized animals. Indomethacin, when administered alone, induces a slight increase in uterine eosinophilia and a slight wet weight increase in the immature rat. In the adult ovariectomized animals, however, these responses to indomethacin are more striking; the uterine wet weight increase is similar to that obtained with estradiol alone.

A significant hyperemia was also observed in the uteri (including the mesometrial tissue) 6 h after treatment with estradiol alone. Indomethacin completely blocked this response.

Discussion. The present results show that prostaglandin biosynthesis inhibition by indomethacin blocks estrogen-induced uterine hyperemia, as previously reported[13-15], but does not block some early non-genomic parameters of estrogen stimulation such as uterine eosinophilia and edema. The effectiveness of prostaglandin biosynthesis inhibition by indomethacin in our experimental conditions is assessed by the presence of effects of prostaglandin inhibition (blockage of estrogen-induced uterine hyperemia, ischemia in the gastrointestinal tract[17]). Therefore, it is possible to speculate that not all early responses to estrogens are mediated by the same mechanism: estrogen-induced uterine hyperemia could possibly be mediated by a prostaglandin-dependent mechanism; uterine eosinophilia and edema seem to be independent of prostaglandin levels. Furthermore, it is possible to conclude that the early non-genomic response to estrogens is not homologous with a non-specific inflammatory response, which is dependent on prostaglandin levels[9]. An explanation for the slight indomethacin-induced uterine eosinophilia and edema remains to be elucidated; it is remarkable, however, that uterine eosinophilia induced in the absence of estrogen is accompanied by edema, a parameter of estrogen stimulation supposed to be mediated by eosinophils.

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