

Synthetic LH-RH as a Possible Stimulator for Secretion of Erythropoietin

Takuma Hashimoto, Hiroya Kawagoe*, Kiyoshi Miyai**,

The Central Clinical Laboratory, Kanazawa University Hospital, Kanazawa.

*The Department of Internal Medicine, National Osaka Hospital and

**The Central Laboratory for Clinical Investigation, Osaka University Hospital, Osaka.

Erythropoietin is the glycoprotein hormone which directly regulates erythropoiesis (1, 2). The regulation of erythropoietin release is considered to be related to the oxygen supply to the kidney and is influenced by several hormones such as testosterone, adrenocorticoids, prolactin, thyroid hormone and growth hormone (GH) (3-5). Also, neurohumoral stimuli are generally believed to result in the release of erythropoietin (6, 7). We describe the increase of reticulocytes and erythropoietin after transnasal administration of synthetic luteinizing hormone releasing hormone (LH-RH) which is a specific stimulator for luteinizing hormone (LH) and follicle stimulating hormone (FSH) from the anterior pituitary.

Materials and methods

Five normal male volunteers aged from 30 to 43 years received 5 mg synthetic LH-RH solution by nasal spray as described previously (8).

The synthetic LH-RH was kindly provided by Daiichi Seiyaku Co., Tokyo, JAPAN. Venous blood samples were collected at -0.5, 0, 0.5, 1, 2, 4, 6, 24, 48 and 72 hours before and after administration of synthetic LH-RH for determination of serum erythropoietin and gonadotropins.

Serum erythropoietin levels were measured by the hemagglutination-inhibition assay described by Lange (9) using a commercial kit. The reagents

were provided by JCI Clinical Research Corporation, Ltd., California, U.S.A. The lower limit of sensitivity in this assay was 1 milli-immunochemical unit per ml. Precision of determination for inter-assay and intra-assay of erythropoietin was 20% and 14% respectively. Normal human serum range in our assay was 15-60 milli-immunochemical units.

Serum gonadotropin and testosterone levels were determined by the double antibody radioimmunoassay as described elsewhere (10). All samples of the serum from a sequential study were run in the same assay in duplicate.

Results

Individual values for serum gonadotropins, testosterone and erythropoietin before and after LH-RH administration in normal subjects are given in Table 1 and Figs. 1, 2.

As shown in Fig. 1, the number of peripheral reticulocytes markedly increased the day after transnasal LH-RH administration and gradually decreased to normal levels by the end of the following 2 weeks.

Serum erythropoietin levels increased significantly in three out of five tested subjects. (Fig. 2)

Gonadotropin responses were significantly increased in all cases. On the other hand, testosterone levels showed no increase after LH-RH

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国立大阪病院内科 川越裕也，大阪大学医学部附属病院中央臨床検査部 宮井 潔。

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administration in these subjects. (Table 1)

Discussion

The onset of this work was that case 3 (T. H: first author) noticed sternalgia 30 minutes after synthetic LH-RH inhale. He thought it might be

brought on by the abnormality of hematopoiesis at the sternum and took examination, and found the number of reticulocytes markedly increased in his blood. He carefully followed up the examination of peripheral blood counts thereafter.

As shown in Fig. 1, the number of peripheral reticulocytes increased the day after transnasal LH-RH administration and gradually decreased to normal levels by the end of the following 2 weeks. Circulating red blood cells increased as well. The sternal pain continued over one week and disappeared. These findings suggest that synthetic LH-RH may influence erythropoietin release, resulting in increase of circulating reticulocytes. Then four other volunteers were tested. As shown in Fig. 2, our results suggest that synthetic LH-RH may be a potent stimulator for secretion of erythropoietin.

Since this drug is a well known specific gonadotropin stimulator (10), the increased erythropoietin might be considered to be mediated by LH and FSH which increased following administration of synthetic LH-RH. But this possibility was neglected, because a patient with hypothalamic

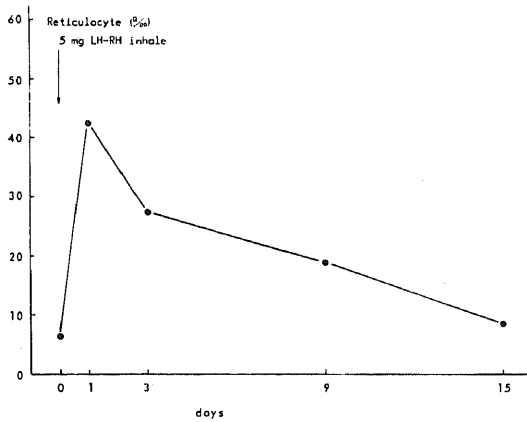


Fig. 1. Increase of circulating reticulocytes (%) after 5 mg LH-RH administration by nasal spray in Case 3.

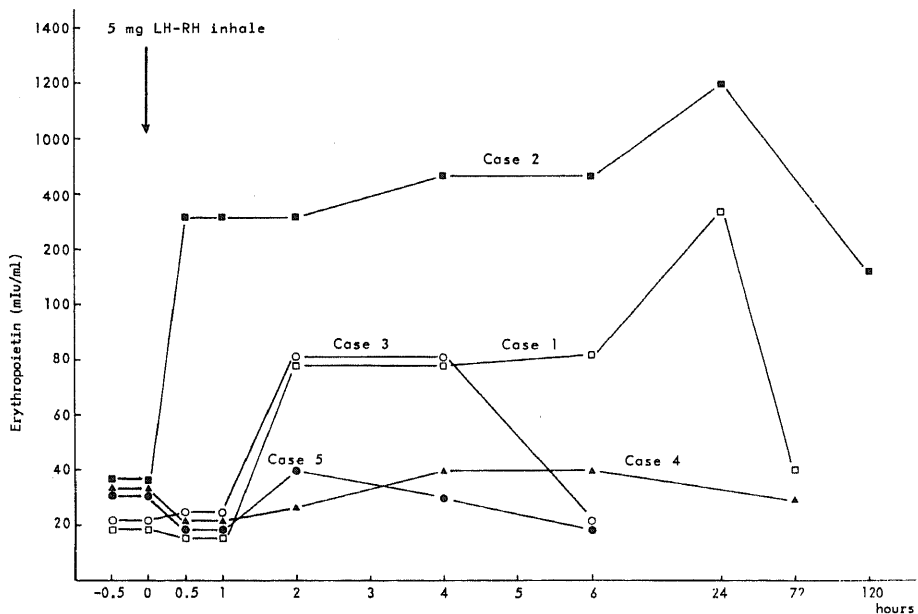


Fig. 2. Serum erythropoietin levels (mIU/ml) after 5 mg LH-RH administration in normal subjects.

Table 1. Serum gonadotropin levels (mIU/ml) and testosterone levels (ng/ml) after 5 mg LH-RH administration by nasal spray

Hormones	Time	Time before and after administration								
	-0.5	0	0.5	1	2	4	6	24	72 hrs	
Serum LH (mIU/ml)	2.9	4.8	59.4*	48.4*	30.6*	17.3*	10.5*	5.4		
	±	±	±	±	±	±	±	±	±	
Mean ± SEM	0.8	1.6	8.3	6.2	1.9	1.1	2.9	0.5		
Serum FSH (mIU/ml)	4.4	4.4	8.8**	10.9**	9.4**	8.9	7.0	2.3		
	±	±	±	±	±	±	±	±	±	
Mean ± SEM	1.5	1.4	2.2	3.4	2.5	2.9	1.3	0		
Serum testosterone (ng/ml)	5.6	5.4	6.0	5.6	5.6	5.4	5.3	5.7	6.7	
	±	±	±	±	±	±	±	±	±	
Mean ± SEM	1.0	0.7	1.0	0.8	0.7	0.8	0.4	0.4	1.6	

* significantly different from basal values ($P < 0.001$)

** $P < 0.05$

hypogonadism revealed a marked erythropoietin response without increase of serum LH and FSH (Hashimoto et al unpublished). Also there was no rise was observed in peripheral testosterone levels as shown in Table 1. These findings suggest that the erythropoietin response to synthetic LH-RH in our study was not mediated by testosterone.

Halvorsen (6) and Feldman et al (7) reported the neurohumoral stimuli resulted in the release of erythropoietin. Our findings may confirm their data. However, an explanation of the reason why all subjects did not respond to synthetic LH-RH in secretion of erythropoietin remains to be elucidated.

Abstract

Increase of circulating reticulocytes was observed in normal male subjects treated with 5 mg synthetic LH-releasing hormone (LH-RH) transnasally. Determination of serum erythropoietin revealed significant increase in these subjects. These findings suggest that LH-RH stimulates erythropoietin secretion and/or influence erythropoiesis.

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抄 録 エリスロポイエチンは造血機構を調節する糖蛋白ホルモンである．従来テストステロン，副腎皮質ホルモン，プロラクチン，甲状腺ホルモン，成長ホルモンなど各種のホルモンがこのエリスロポイエチンの分泌に影響を及ぼすことが報告されてきた．さらに Halvorsen や Feldman らは神経内分泌学的因子がその分泌に関与することを報告している．我々は，5人の男子に経鼻的に 5mg の合成 LH-releasing hormone (LH-RH) を投与した時胸痛と末梢血中の網赤血球数の一過性増加及びそれにつづく赤血球増多症がみられることを観察した．そこでその原因としてエリスロポイエチンの関与の可能性を JCI のキットを用いて検討したところ5人中3人に著明な増加反応を認めた．さらに経時的採血した検体中にテストステロン等上記の各種ホルモンの非特異的増加はみられなかった．

以上の成績より視床下部ホルモンの1つである LH-RH が直接エリスロポイエチンの分泌を促進した可能性が示唆された．しかし，全例にエリスロポイエチンの増加反応がみられなかった理由については現在のところ不明である．