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Mechanism of growth hormone insensitivity induced by endotoxin[1]

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KEY WORDS somatotropin; somatotropin receptors; insulin-like growth factor Ⅰ; lipopolysaccharides; interleukin-6; tumor necrosis factor; enzyme-linked immunosorbent assay; reverse transcriptase polymerase chain reaction

ABSTRACT

AIM: To investigate the mechanism of growth hormone (GH) insensitivity induced by endotoxin at receptor and post-receptor levels. **METHODS**: Sprague-Dawley rats were injected endotoxin along with or without GH administration. The liver expression of insulin-like growth factor Ⅰ (IGF-Ⅰ), GH receptor (GHR), and suppresor of cytokine signaling (SOCS)-3 mRNA were detected by reverse transcriptase polymerase chain reaction, the GH levels were measured by radioimmunoassay, the levels of tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) were detected by enzyme-linked immunosorbent assay. **RESULTS**: Serum GH levels had no significant difference compared with control rats after endotoxin injection, however, liver IGF-Ⅰ mRNA expression was obviously down-regulated in endotoxemic rats. Liver GHR mRNA expression was predominantly down-regulated after LPS injection; although SOCS-3 mRNA was weakly expressed in control rats, it was strongly up-regulated in endotoxemic rats. Endotoxine stimulated the production of TNF-α and IL-6, and the elevated IL-6 levels showed a positive correlation with increased SOCS-3 mRNA expression. Exogenous GH could enhance IGF-Ⅰ mRNA expression in control rats, but it did fail to prevent the decline in IGF-Ⅰ mRNA expression in endotoxemic rats. Two different LPS dosages (7.5 mg/kg and 5.0 mg/kg) produced the same down-regulation of IGF-Ⅰ mRNA expression, however, the higher LPS dosage induced more GHR mRNA down-regulation and more SOCS-3 mRNA up-regulation. **CONCLUSION**: The mechanism of growth hormone insensitivity induced by endotoxin was associated with down-regulated GHR mRNA expression at receptor level and up-regulated SOCS-3 mRNA expression at post-receptor level. The inhibition at post-receptor level had close relationship with the increased IL-6 secretion.

INTRODUCTION

Infection especially severe intra-abdominal infection is characterized by catabolic state associated with severe protein loss and negtive nitrogen balance[1]. Meantime, the levels of many important hormones such as glucocorticoid, insulin, and growth hormone (GH) do not decline, but their biological activities have reduced obviously. Critical illness such as sepsis, trauma, and burns cause an elevated growth hormone level at early stage, but the insulin-like growth factor Ⅰ (IGF-Ⅰ), which is a growth hormone-dependent growth factor that inhibits protein breakdown, has decreased predominantly, this phenomenon indicates a state of growth hormone insensitivity[2,3]. In this condition, the administration of high doses of recombinant human growth hormone could not improve negative nitrogen balance, in contrary, it maybe lead to other metabolic disorders and result in increased morbidity and mortality[4].

Endotoxin is generously released into blood under the infected condition, and it plays a very important role in inducing the growth hormone insensitivity. It will give some helps to overcome this unfavourable condition in clinical works to understand the detailed mechanism of GH insensitivity induced by endotoxin. In this study, we investigate the mechanisms that might be responsible for the GH insensitivity induced by endotoxin at receptor and post-receptor levels.

MATERIALS AND METHODS

Endotoxin and hormone preparation

Escherichia coli lipopolysaccharide (LPS; stereotype

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O111: B4 phenol extract), obtained from Sigma Chemical Co, was resuspended in sterile endotoxin-free saline to obtain a 4 g/L solution. Human GH, kindly provided by Serono, was resuspended in sterile endotoxin-free saline to obtain a 1 g/L solution.

Experimental protocols Male Sprague-Dawley rats (provided by Animal Center of Jingling Hospital, Grade Ⅱ, Certificate number 003), weighing (250 ± 10) g, were given free access to food and water for 3 d before experiments. Rats were anesthetized with ether and received LPS, GH, or saline injection. LPS was administered through superficial dorsal veins of penis and GH was injected subcutaneously. All rats were killed at different time points. Blood was collected and centrifuged at 500 × *g* for 10 min at 4 ℃ to comlect serum. Livers were removed, flash-frozen in liquid nitrogen, and stored at −80 ℃ until homogenate preparation and RNA extraction.

Experiment 1: effect of LPS on liver expression of IGF-Ⅰ, GHR, and suppressor of cytokine signaling (SOCS)-3 mRNA After 3-d adaptation period, 42 rats were randomly divided into laboratory group (n = 36) and control group (n = 6). LPS (7.5 mg/kg, iv) was administered to the laboratory group, every six rats were killed at 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h after injection. The control rats were given saline intravenously.

Experiment 2: effect of different LPS dosages on liver expression of IGF-Ⅰ, GHR, and SOCS-3 mRNA and on IGF-Ⅰ response to GH After 3-d adaptation period, 36 rats were divided into 6 groups (6 rats/group). The first group received one injection of LPS (7.5 mg/kg, iv) and one injection of saline (sc), the second group received one injection of LPS 5.0 mg/kg and one injection of saline (sc), the third group received one injection of GH (1.5 mg/kg, sc) and one injection of saline (iv), the fourth group received one injection of LPS (7.5 mg/kg, iv) and one injection of GH (1.5 mg/kg, sc), the fifth group were given lower dosage of LPS (5.0 mg/kg) and one injection of GH (1.5 mg/kg), the sixth group received two injections of saline. All rats were killed at 10 h after injection.

Primers The reverse transcriptase polymerase chain reaction (RT-PCR) primers for IGF-Ⅰ, GHR, and SOCS-3 were designed according to the published sequences in Tab 1 and were synthesized by Sangon Co (Shanghai).

RNA extraction and RT-PCR Total RNA was extracted using TRIZOL reagent (Gibco BRL Co). With access RT-PCR system kit (Promega Co), the cDNA synthesis and amplification was done in one tube following the manufacture's instructions. In brief, RNA 1 μg, primers 1 μmol/L for SOCS-3, GHR, and IGF-Ⅰ were added to each reaction mixture respectively, which included dNTP 0.2 mmol/L, $MgSO_4$ 1 mmol/L, AMV reverse transcriptase 5 U, Tfl DNA polymerase 5 U, and AMV/Tfl 5 × buffer 10 μL. The reaction final volume was 50 μL and was covered with 30 μL mineral oil. RT-PCR reaction was run in the following procedures: 1) Reverse transcription: 48 ℃ for 45 min, 1 cycle. 2) AMV RT inactivation and RNA/cDNA/primers denaturation: 94 ℃ for 2 min, 1 cycle. 3) Second strand cDNA synthesis and PCR amplification: denaturation at 94 ℃ for 30 s, annealing at 60 ℃ for 1 min, extension at 68 ℃ for 2 min, 28 cycles for SOCS-3 and 21 cycles for GHR and IGF-Ⅰ. 4) Final extension: 68 ℃ for 7 min, 1 cycle. PCR product 5 μL was run on 1.7 % agarose gel and observed by EB staining under UV light. The images were taken by Kodak digital camera and were analyzed with 1D image analysis software. The level of IGF-Ⅰ and GHR were expressed as percentages of density, and SOCS-3 mRNA were expressed as folds of density compared with control group.

Rat growth hormone assay Serum growth hormone levels were measured by radioimmunoassay method, and the kit was provided by Northern Isotope Co (Beijing).

Tab 1. PCR primer sequences and expected size of amplified products.

Primers	Sequence	Size
SOCS-3 upstream	5′ ACC AGC GCC ACT TCT TCA CG 3′	
SOCS-3 downstream	5′ GTG GAG CAT CAT ACT GAT CC 3′	150 bp
GHR upstream	5′ CTG GGT TGA GTT CAT TGA GCT GGA T 3′	
GHR downstream	5′ TGT AGA GGG GAG TTG GTG GGT TGA C 3′	394 bp
IGF-Ⅰ upstream	5′ CAC ATC TCT TCT ACC TGG CAC TC 3′	
IGF-Ⅰ downstream	5′ GGA TGG AAC GAG CTG ACT TTG TA 3′	270 bp

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Rat tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) assay Serum TNF-α and IL-6 levels were detected using an enzyme-linked immunoabsorbent assay (ELISA). Rat TNF-α kit was provided by DiaClone Co (France) and rat IL-6 kit came from Biosource Co (USA)

Statistical analysis Comparisons between data from control and laboratory groups was performed by *t* test. Correlation between data was analyzed with linear regression. Statistics analysis was conducted with SPSS statistical software. Results were considered statistically significant at $P < 0.05$.

RESULTS

Levels of serum growth hormone after LPS injection The levels of serum growth hormone at each time points after LPS injection had no significant difference compared with control rats (Tab 2).

Tab 2. Changes in serum GH levels after LPS (7.5 mg/kg) injection. $n = 6$. $\bar{x} \pm s$. $^aP > 0.05$ *vs* control.

Group	GH concentration/mg·L^{-1}
Control	2.2 ± 0.5
1 h	1.8 ± 0.4[a]
2 h	2.0 ± 0.4[a]
4 h	1.76 ± 0.27[a]
8 h	1.79 ± 0.27[a]
12 h	1.77 ± 0.20[a]
24 h	1.8 ± 0.6[a]

Levels of serum TNF-α and IL-6 after LPS injection After single LPS (7.5 mg/kg, iv) injection, the levels of serum TNF-α and IL-6 increased rapidly, however, TNF-α had an abruptly decrease at 2 h (Tab 3). The TNF-α levels were all below 20 ng/L in six groups at 10 h after LPS 7.5 and 5.0 mg/kg iv injection, but for IL-6, LPS 7.5 mg/kg stimulated more IL-6 secretion than LPS 5.0 mg/kg. GH injection did not affect the IL-6 levels.

Liver IGF-Ⅰ mRNA expression Liver IGF-Ⅰ mRNA expression declined by 25 % *vs* control rats at 8 h after LPS 7.5 mg/kg injection. After 12 h, the most down-regulation was observed, which was a 53 % decrease compared with control rats (Fig 1A). The down-regulation of IGF-Ⅰ mRNA expression had no difference between LPS 7.5- and 5.0 mg/kg-treated group. Although exogenous GH administration in control rats markedly enhanced the liver IGF-Ⅰ mRNA expression, it did fail to prevent its decline in endotoxemic rats (Fig 1B).

Tab 3. Changes in serum TNF-α and IL-6 levels after LPS 7.5 mg/kg injection. $n = 6$. $\bar{x} \pm s$.

Group	TNF-α level/ng·L^{-1}	IL-6 level/ng·L^{-1}
Control	< 20	< 8
1 h	343 ± 50	1 439 ± 323
2 h	76 ± 12	1 678 ± 127
4 h	< 20	1 333 ± 121
8 h	< 20	143 ± 48
12 h	< 20	49 ± 11
24 h	< 20	47 ± 12

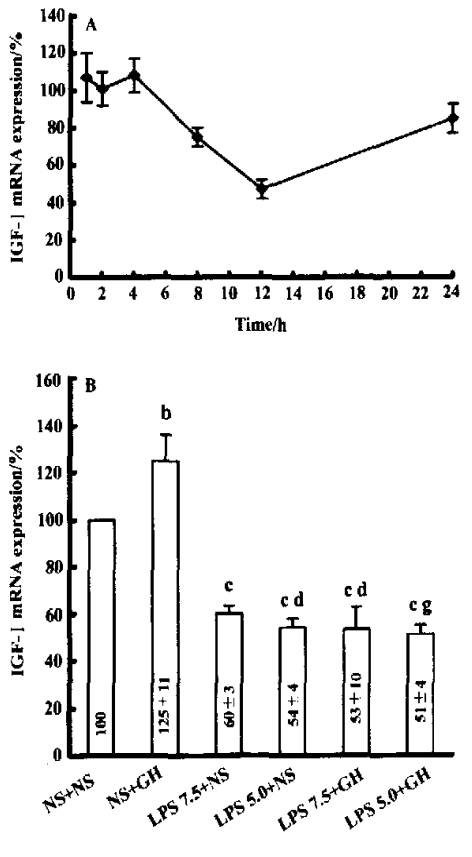

Fig 1. A) Liver IGF-Ⅰ mRNA expression reponse to LPS (7.5 mg/kg) iv injection at different time points. B) Liver IGF-Ⅰ mRNA expression after single GH 1.5 mg/kg injection with or without LPS 7.5 and 5.0 mg/kg. $n = 4$. $\bar{x} \pm s$. $^bP < 0.05$, $^cP < 0.01$ *vs* NS + NS group. $^dP > 0.05$ *vs* LPS 7.5 mg/kg + NS group. $^dP > 0.05$ *vs* LPS 5.0 mg/kg + NS group.

Liver GHR mRNA expression Liver GHR mRNA expression began to decrease at 2 h and the most decrease occurred at 8 h after LPS 7.5 mg/kg injection, which was a 81 % decrease compared with control rats (Fig 2A). The more reduction of liver GHR mRNA expression was observed in rats injected with LPS 7.5 mg/kg than LPS 5.0 mg/kg; the exogenous GH administration had no effect on the liver GHR mRNA expression in control and endotoxemic rats (Fig 2B).

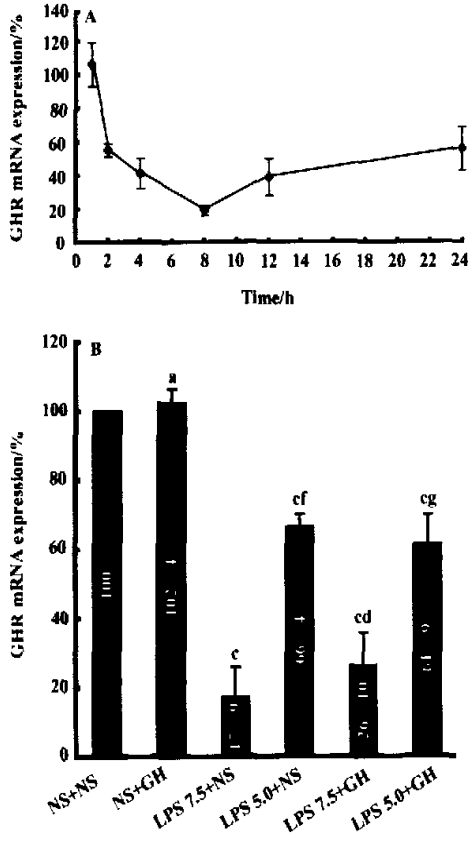

Fig 2. A) Liver GHR mRNA expression reponse to LPS 7.5 mg/kg iv injection at different time points. B) Liver GHR mRNA expression after single GH (1.5 mg/kg) injection with or without LPS 7.5 and 5.0 mg/kg. $n = 4$. $\bar{x} \pm s$. $^aP > 0.05$, $^cP < 0.01$ *vs* NS + NS group. $^dP > 0.05$, $^fP < 0.01$ *vs* LPS 7.5 mg/kg + NS group. $^gP > 0.05$ *vs* LPS 5.0 mg/kg + NS group.

Liver SOCS-3 mRNA expression Liver SOCS-3 mRNA was weakly expressed in control rats, however, it was strongly up-regulated by 7.84 times *vs* control rats at 1 h after LPS injection, this level was maintained at 2 h and it was still as 1.8 times as control at 24 h (Fig 3A). The more up-regulation of liver SOCS-3 mRNA expression was associated with the higher dosage of LPS injection, the exogenous GH infusion had no effect on the liver SOCS-3 mRNA expression in control and endotoxemic rats (Fig 3B).

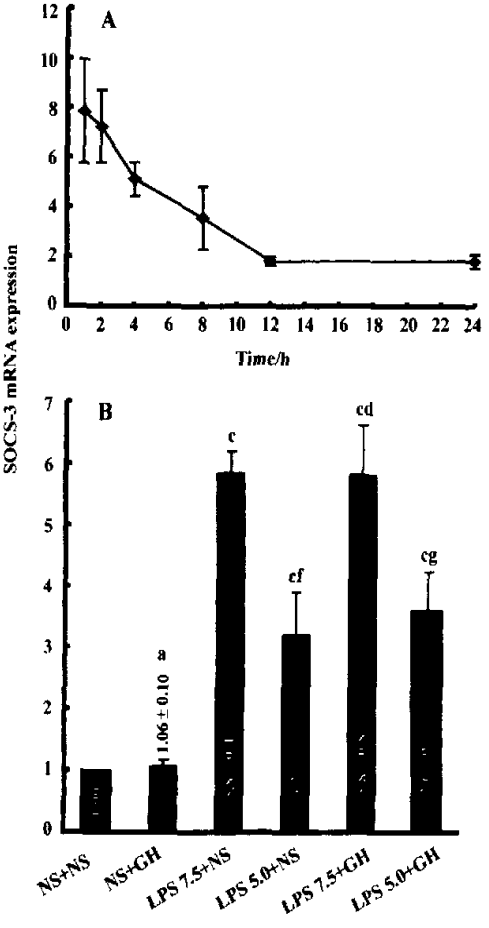

Fig 3. A) Liver SOCS-3 mRNA expression reponse to LPS 7.5 mg/kg iv injection at different time points. B) Liver SOCS-3 mRNA expression after single GH 1.5 mg/kg injection with or without LPS 7.5 and 5.0 mg/kg. $n = 4$. $\bar{x} \pm s$. $^aP > 0.05$, $^cP < 0.01$ *vs* NS + NS group. $^dP > 0.05$, $^fP < 0.01$ *vs* LPS 7.5 mg/kg + NS group. $^gP > 0.05$ *vs* LPS 5.0 mg/kg + NS group.

Correlation between liver GHR and SOCS-3 mRNA expression and IL-6 concentration After LPS iv injection, no correlation was found between liver GHR mRNA expression and IL-6 levels ($r = 0.509$, $P > 0.05$). Linear regression analysis showed a positive correlation of IL-6 levels with liver SOCS-3 mRNA expression ($r = 0.935$, $P < 0.01$).

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DISCUSSION

In this report, using experimental method of *E coli* endotoxin infusion in laboratory rats, we have found endotoxin-induced growth hormone insensitivity. In experiment one, serum GH levels in endotoxemic rats had no difference compared with control rats, but liver IGF-Ⅰ mRNA expression declined obviously. In experiment two, the liver IGF-Ⅰ mRNA expression was up-regulated by 25 % after exogeous GH administration in control rats, but in endotoxemic rats, GH did fail to prevent the decline in liver IGF-Ⅰ mRNA expression. Several groups have observed that decreased IGF-Ⅰ maybe result from a state of GH insensitivity. Ross *et al*[3] reported low circulating IGF-Ⅰ levels in critically ill patients despite elevated GH secretion. More recently, Fan *et al*[5] showed that after a single injection of LPS in rats, plasma IGF-Ⅰ levels remained low despite the fact that GH level had returned to normal value. In agreement with these authors, our study supports the possibility that endotoxin maybe one of the important factor in inducing the GH insensitivity under the septic state.

GH insensitivity can occur at receptor and post-receptor levels, the receptor level is associated with the reduced GHR numbers on target cell surface[6,7]. Because the shorter half-life of liver GHR (30 – 40 min) and the decreased liver GHR mRNA expression by endotoxin, which led to the reduced GHR synthesis[8,9]. Our results showed that liver GHR mRNA expression was obviously down-regulated after endotoxin injection and the more decrease was associated with the higher dosages infusion, these manifested that endotoxin could reduce GHR synthesis indeedly.

Post-receptor level GH resistance caused more and more attenuation recently, and it is associated with a novel family of SOCS, which includes eight members (SOCS-1 to SOCS-7 and CIS) and acts in a classical negative feedback loop to regulate cytokine signal tranduction[10]. SOCS-3 is a strong inhibitor on growth hormone intracellular signal transduction[11].

Once GH binds to its receptor, the intracellular signal transduction is activated through JAK-STAT pathway[12,13]. The first activated tyrosine kinase is JAK2, which promotes the tyrosyl phosphorylation of both JAK2 itself and signal transducer and activator of transcription 5b (STAT5b). The phosphorylated STAT5b causes its dimerization and then the dimerized STAT5b translocates into nucleus, there, it binds with high affinity to the promoters of various target genes and then activates the gene transcription such as IGF-Ⅰ. SOCS-3 can block the GH intracellular JAK/STAT-dependent signaling pathway at different levels[14-18], including: 1) Competitively inhibits the phosphorylation of STAT5b; 2) Binds to GHR and leads to the degradation of GHR-JAK2 compound directly or indirectly through elongin B and elongin C, in the end, the JAK2 kinase loses its activity; 3) Through binding to GHR, SOCS-3 can inhibit the activity of JAK2 kinase directly. Our experiment observed that after endotoxin injection, liver SOCS-3 mRNA expression was rapidly up-regulated and higher dosage of endotoxin was associated with higher increased SOCS-3 mRNA expression. In experiment two, we also found that although higher dosage of endotoxin led to more reduced GHR mRNA expression and more elevated SOCS-3 mRNA expression, the liver IGF-Ⅰ mRNA expression had no difference between the two dosages. This phenomenon could not be explained only by one factor, the decreased GHR mRNA expression might be coupled with the elevated SOCS-3 mRNA expression to regulate the IGF-Ⅰ mRNA expression at two different levels.

The *in vivo* biological activities of LPS are largely mediated by the production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6)[19,20]. In our study, endotoxin stimulated a transient TNF-α secretion and a relatively continued IL-6 release. The elevated IL-6 levels showed a positive correlation with liver SOCS-3 mRNA expression. The mechanisms of endotoxin induced GHR mRNA down-regulation have not been revealed, but the effect of endotoxin on SOCS-3 mRNA expression might be mediated through IL-6. Both IL-6 and GH belong to the cytokine receptor superfamily, they transduce their signal from cell surface to nucleus through the same JAK-STAT pathway[21,22]. Hence, the increased IL-6 secretion might up-regulate the expression of SOCS-3 mRNA, which not only had a negative feedback to IL-6 biological activities, but also inhibited the GH intracellular signal transduction[23,24].

In summary, GH insensitivity was associated with the endotoxin levels under the septic state, which occured at receptor and post-receptor levels at the same time. In this condition, exogeous GH administration did not produce positive effect on the illness, and the most important thing to recover the GH sensitivity was to take some measures to reduce the production of endotoxin and

cytokines.

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内毒素诱导生长激素不敏感的机制[1]

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关键词 生长激素; 生长激素受体; 胰岛素样生长因子Ⅰ; 脂多糖类; 白介素-6; 肿瘤坏死因子; 酶联免疫吸附测定; 逆转录聚合酶链反应

目的: 从受体和受体后水平探讨内毒素诱导的生长

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激素(GH)不敏感的发生机制. **方法**: 采用 SD 大鼠, 静脉和皮下分别或同时注射 LPS 和 GH. 用逆转录聚合酶链反应测定肝组织胰岛素样生长因子-Ⅰ(IGF-Ⅰ), 生长激素受体(GHR)和细胞因子信号传导抑制子-3 (SOCS-3) mRNA 的表达; 用放免法测定血清 GH 水平; 用酶联免疫吸附测定法测定血清肿瘤坏死因子 α (TNF-α)和白介素-6 (IL-6)水平. **结果**: 注射 LPS 后血清 GH 水平与对照组均无明显差异, 但肝组织 IGF-Ⅰ和 GHR mRNA 的表达明显下调; 正常鼠肝组织 SOCS-3 mRNA 微弱表达, 注射 LPS 后显著上调. LPS 刺激 TNF-α 和 IL-6 的释放, IL-6 升高的水平与 SOCS-3 mRNA 表达的上调成高度正相关. 对照组大鼠注射外源性 GH 后肝组织 IGF-Ⅰ mRNA 的表达明显上调, 但它不能阻止内毒素血症鼠 IGF-Ⅰ mRNA 表达的下降. 两种剂量的 LPS (7.5 mg/kg 和 5.0 mg/kg)注射产生同样的 IGF-Ⅰ mRNA 下调水平, 但大剂量 LPS 注射诱导更多的 GHR mRNA 的表达下调和 SOCS-3 mRNA 的表达上调. **结论**: 内毒素诱导的生长激素不敏感的机制在受体水平与 GHR mRNA 的表达下调有关, 在受体后水平与 SOCS-3 mRNA 的表达上调有关. 受体后水平的抑制与 IL-6 分泌的增加密切相关.

(责任编辑 朱倩荟)

Announcement

As Acta Pharmacologica Sinica has been changed into English publication, according to the China governmental regulation for publishing, the ISSN of APS has been given a new code number. The number is 1671-4083. The former ISSN 0253-9756 is cancelled. Please pay attention to this change for your indexing systems.