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# NEONATALY APPLIED SRIH-14 HAS IMMEDIATE AND PROLONGED INHIBITORY EFFECT ON PITUITARY GH CELLS

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*The immediate and prolonged effects of neonatal SRIH-14 treatment on pituitary somatotrophs (GH) were investigated. Female rats were injected s.c. twice a day with 20 μg of SRIH-14/100g b.w., for five consecutive days (from 3rd to 7th day of life). Animals were sacrificed at different life periods: at neonatal (8th day), juvenile (16th day), peripubertal (38th day) and adult (80th day) period of life. GH cells were studied using the peroxidase-antiperoxidase immunocytochemical procedure. Morphometry and stereology were used to evaluate changes in the number of GH-immunoreactive cells per unit area, their volume and volume density. After SRIH-14 treatment, the most prominent decrease of all measured parameters was observed in the neonatal period. SRIH-14 induced a significant decrease of GH cell volumes and volume densities in the juvenile, peripubertal and adult periods of life. The number of GH-positive cells was significantly decreased when examined immediately after treatment, but significantly increased in adult females. Body weight, absolute or relative pituitary weights were not affected in any of the examined age groups. These findings suggest that neonatal SRIH-14 treatment exerts a significant immediate and prolonged inhibitory effect on GH cells, but does not affect the growth rate in female rats.*

*Key words: female rats, somatostatin, somatotrophic cells, development*

## INTRODUCTION

The secretion of somatotrophin, or growth hormone (GH), is regulated through a complex neuroendocrine control system that comprises two main hypothalamic regulators, growth hormone releasing hormone (GHRH) and somatostatin (SRIH), exerting stimulatory and inhibitory influences, respectively, on the somatotrophic (GH) cells. Circulating GH concentrations are age-dependent in all mammalian species studied to date. GH levels are particularly high in the fetus and neonatal period, and decline during the juvenile period of life.

During puberty, GH levels rise and then fall during senescence. This pattern has been observed in rats (Rieutort, 1974; Ojeda and Jameson, 1977; Walker, *et al*., 1977; Sonntag *et al.,* 1980; Szabo and Cuttler, 1986; Welsh *et al*., 1986), humans (Finkelstein *et al*., 1972; Rudman *et al*., 1981), and other mammals (Gluckman *et al.*, 1981). In contrast to circulating GH levels, pituitary GH concentrations are characteristically low in the fetus, steadily increase during maturation, and then decline later in life (Rieutort, 1974; Hu *et al*., 1993).

In the pituitary, SRIH inhibits GH secretion and also blocks the release of other adenohypophyseal hormones such as thyrotrophin (TSH; Brazeau *et al.,* 1973) prolactin (PRL; Milošević *et al*., 2000), gonadotrophins (Nestorović *et al*., 2001, 2004) and in some cases, adrenocorticotropin (ACTH; Starčević *et al*., 2000). Since its characterization in 1973 (Brazeau *et al.,* 1973), SRIH has attracted much attention because of its wide variety of biological functions in the nervous and other tissues. At the periphery, SRIH is a modulator of endocrine and exocrine functions and regulates differentiation and proliferation of normal and tumor cells (Reichlin, 1983; Patel, 1999). Within the nervous system, SRIH acts as a neuromodulator with physiological effects on neuroendocrine, motor and cognitive functions (Reichlin, 1983; Epelbaum *et al*., 1994). Because of its ability to inhibit many functions of various organs, its therapeutic value in clinical conditions involving the hyperfunction of these organs, is recognized and used. However, since SRIH has a wide variety of actions, it has been cautiously used in pediatric cases.

We have previously shown that multiple SRIH-14 treatment decreased morphometric parameters of GH cells in adult female rats (Milošević *et al*., 2002). The aim of this study was to investigate whether multiple neonatal SRIH-14 treatment has immediate or/and prolonged effects on pituitary GH cells in female rats.

## MATERIAL AND METHODS

*Animals*. Time-mated pregnant Wistar rats were housed individually and maintened in a controlled environment (12h light : 12 h dark; 22 ± 2 $^{o}$C), with food (produced by Veterinarski zavod Subotica, Subotica, Sebia) and water *at libitum*. Female pups were injected s.c. twice a day (8 AM and 8 PM) with 20 μg of SRIH-14 (S9129, Sigma, St. Louis, Mo., USA) per 100g b.w., for five consecutive days (3$^{rd}$ to 7$^{th}$ days of life; neonatal SRIH-14 treatment). The dose regimen selected for SRIH-14 was based on Rebuffat *et al*. (1984) and modified for administration every 12 h instead of every 8 h. Control female pups s.c. received the equivalent volume of saline by the same schedule. Animals were sacrificed at 8 AM at different periods of life: at neonatal (8$^{th}$ day), juvenile (16$^{th}$ day), peripubertal (38$^{th}$ day) and adult (80$^{th}$ day) period of life. Every age group comprised five females. Experimental protocols were approved by the Local Animal Care Committee and conformed to the recommendations given in "Guide for the Care and Use of Laboratory Animals" (1996, National Academy Press, Washington D.C.)

*Immunocytochemistry.* The pituitaries were removed immediately after sacrifice and fixed in Bouin's solution for 48 hours at room temperature. After

dehydration in an ethanol gradient, organs were embedded in paraffin. Series of seven sections (5 μm) of the pituitary cut through three tissue levels (dorsal, middle and ventral portion) of the *pars distalis* were used for immunostaining. For the localization of pituitary somatotrophs the peroxidase-antiperoxidase method was used (Sternberger, 1970). After deparaffinization and rehydration of sections, endogenous peroxidase activity was blocked by incubation in methanol containing 0.3% $H_2O_2$ for 15 minutes at room temperature, followed by rinsing in 0.1 M phosphate buffered saline (PBS; pH 7.4) for 5 minutes. The non-specific background staining was reduced by incubation with non-immune serum, i.e. normal porcine serum diluted 1:10 with PBS for 45 minutes. The sections were than incubated overnight with primary antibodies (hGH antisera - DAKO A/S, Glostrup, Denmark) diluted with PBS 1:300. Subsequent to a 5 minute rinse in PBS, the sections were incubated with secondary antibody (1:500 swine-anti-rabbit IgG, 45 min; DAKO A/S, Glostrup, Denmark), rinsed for 5 minutes in PBS, incubated with rabbit-antiperoxidase serum (1:100; 45 min; DAKO A/S, Glostrup, Denmark) and again rinsed in PBS. The antigen-antibody complex was visualized by incubating the sections with chromogen substrate, 0.05% 3,3-diaminobenzidine (DAB; Serva, Heidelberg, Germany) and 0.03% $H_2O_2$. The incubated sections were counterstained with haematoxylin. Control sections were incubated with normal porcine serum without primary antisera.

*Stereological measurements.* Immunocytochemically stained sections of pituitaries cut through three tissue levels of the *pars distalis* were used for the morphometric examinations of GH immunoreactive cells with visible nuclei. The cell volume of GH cells (Vc) and their volume densities ($V_V$) were estimated under light microscope at 1000X magnification using the $M_{42}$ multipurpose test system (Weibel, 1979). The volumes of GH-positive cells were expressed in $\mu m^3$, while their volume densities were given as percentages of total pituitary cells in $mm^3$. At the same time, the number of immunoreactive cells per unit area ($mm^2$) in each section was analyzed.

*Statistical analyses*. The data obtained for each group were averaged and the standard deviation was calculated. A one-way analysis of variance (ANOVA), followed by multiple range test of Duncan was used for statistical comparisons of the differences between groups. A probability value of 5% or less was considered statistically significant.

## RESULTS

Somatotrophic (GH) cells of the control females in all examined age groups were strongly immunocytochemically stained. They were polygonal, oval or polyhedral in shape with prominent, often eccentrically located nuclei. GH-positive cells were grouped and positioned throughout the pituitary *pars distalis*, often in close contact with the blood capillaries (Figs. 1a-d). It has been noted that GH cells of adult females were larger, with more homogenously immunostained cytoplasm compared to the earlier periods of life (Figs. 1a-d). After neonatal SRIH-14 treatment GH cells were smaller in all examined age groups (Figs. e-h). In the pituitaries of neonatal females GH-positive cells were smaller in size and fewer in

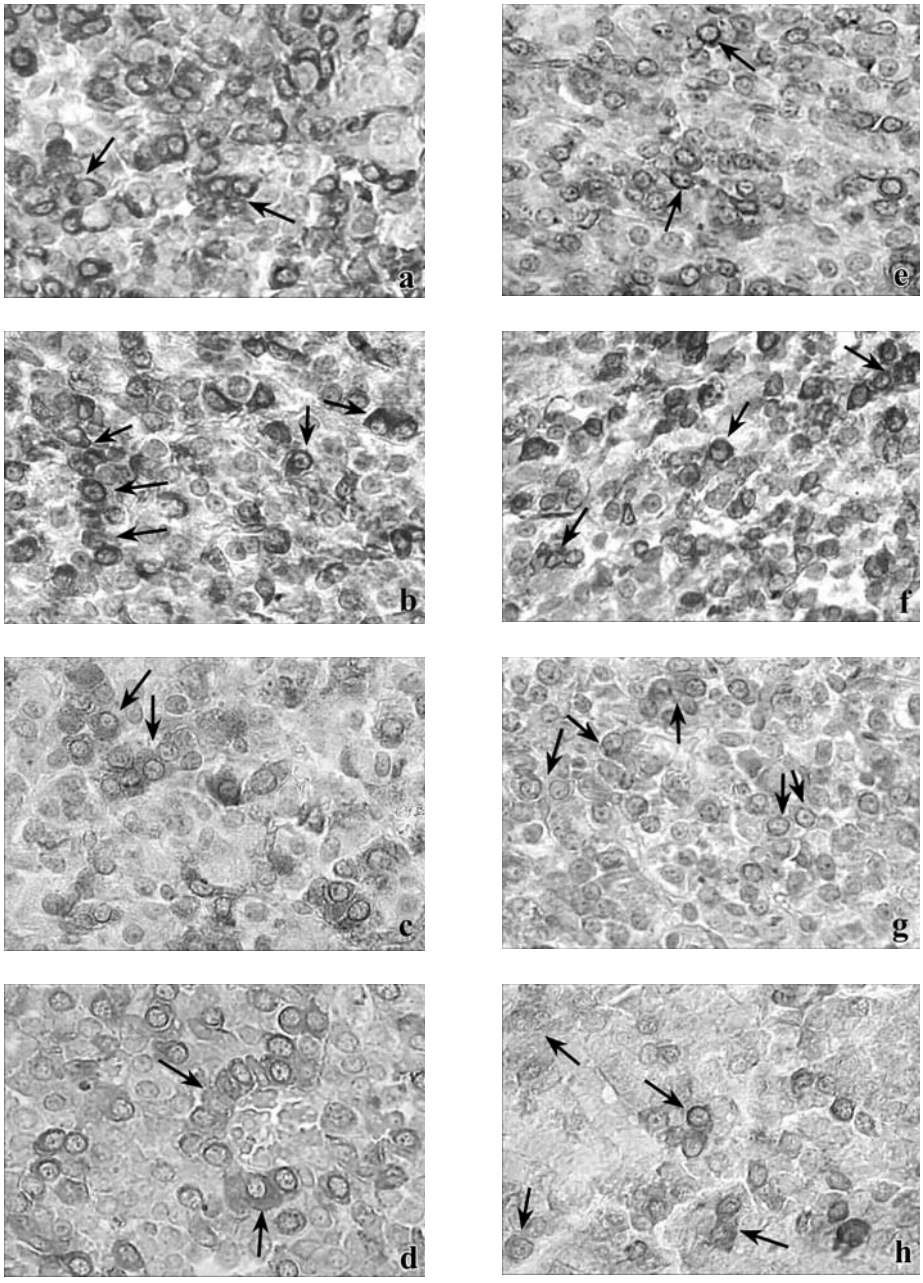


Figure 1. Immunoreactive GH cells (arrows) in pituitary pars distalis in control (a-d) and female rats after neonatal SRIH-14 treatment (e-h) of neonatal (a, e), juvenile (b, f), peripubertal (c, g) and adult (d, h) period of life

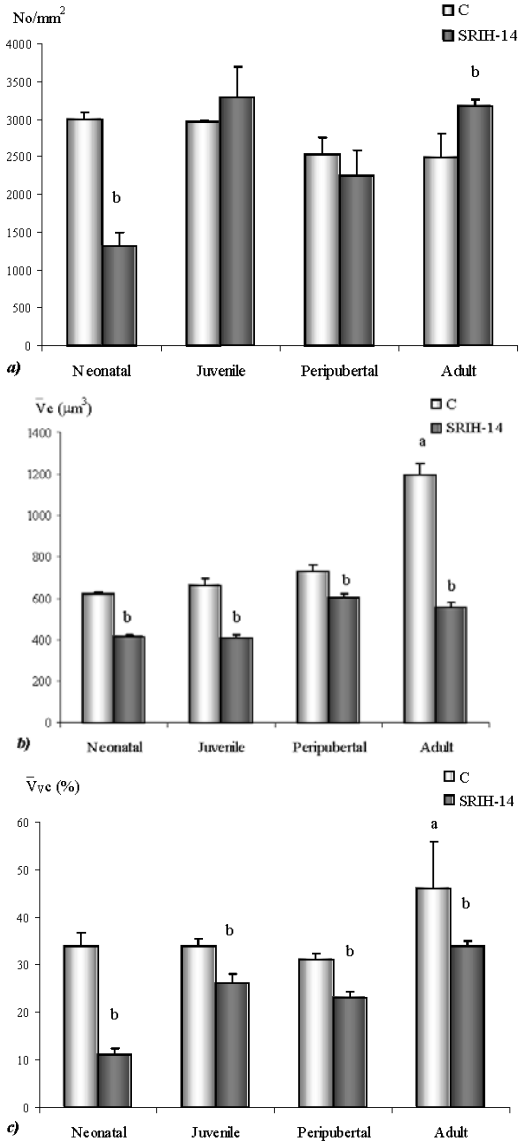


Figure 2. a) The number (No) of immunoreactive GH cells per unit area ($mm^2$) in control (C) and female rats after neonatal SRIH-14 treatment; b) The cellular ($\overline{V}c$) volume ($\mu m^3$) of GH-immunopositive cells of control (C) and female rats after neonatal SRIH-14 treatment; c) Volume density ($\overline{V}_V$) of immunoreactive GH cells expressed as a percentage (%) of total adenohypophyseal cells volume in control (C) and female rats after neonatal SRIH-14 treatment. All values are given as means ±SD. $^{a}p<0.05$ vs. control from previous period of life; $^{b}p<0.05$ vs. corresponding control

number. Their cytoplasm was more intensely immunostained than in the neonatal controls, forming a thin ring around the nuclei (Fig. 1e). The cytoplasm of GH-positive cells in the pituitaries of peripubertal and adult females was weakly immunstained (Figs. 1g-h).

The number of GH-immunopositive cells per unit area ($mm^2$) in the pituitaries of control females did not change from neonatal until the juvenile period, but decreased thereafter from juvenile until the adult period of life (Fig 2a). The volume of GH cells increased during the investigated periods. The most prominent increase (by 64.7%; $p<0.05$) was observed from the peripubertal until the adult period of life (Fig. 2b). In the same period the volume density of GH cells increased by 48.4% ($p<0.05$; Fig. 2c).

After neonatal SRIH-14 treatment the number of GH-immunoreactive cells per unit area was markedly decreased in 8-day old females (by 56.2%; $p<0.05$) in comparison to the neonatal controls. In 16 and 38 days old neonataly treated females, this parameter was similar to the values of corresponding controls. However, in adult females the number of GH-immunopositive cells was by 25.7% ($p<0.05$) higher than in adult controls (Fig. 2a).

Stereological analysis showed that the neonatal SRIH-14 treatment significantly decreased the volume of GH cells in all examined age groups (Figs. 2b, c). In the neonatal, juvenile and peripubertal periods of life, this parameter was decreased by 33.5%, 38.5%, 17.1%, respectively, when compared to the corresponding controls. The most prominent decrease of GH cell volume was noted in the adult age group (by 53.8%; $p<0.05$).

Table 1. Body weight, absolute and relative pituitary weight of control (C) and female rats at different periods of life after neonatal SRIH-14 treatment

| Groups | | Body weight (g) | Absolute pituitary weight (mg) | Relative pituitary weight (mg%) |
|---|---|---|---|---|
| Neonatal | C | 17.8 ± 0.7 | 2.0 ± 1.0 | 11.2 ± 5.4 |
| | SRIH-14 | 16.1 ± 1.8 | 1.8 ± 0.8 | 11.6 ± 5.3 |
| Juvenile | C | 27.2 ± 0.4 | 2.5 ± 0.6 | 9.2 ± 2.0 |
| | SRIH-14 | 22.9 ± 2.0 | 2.4 ± 0.9 | 10.3 ± 3.8 |
| Peripubertal | C | 117.4 ± 8.6 | 5.6 ± 0.9 | 4.8 ± 0.8 |
| | SRIH-14 | 130.0 ± 0.7 | 5.4 ± 1.1 | 4.2 ± 0.9 |
| Adult | C | 255.0 ± 20.7 | 11.8 ± 2.3 | 4.6 ± 0.7 |
| | SRIH-14 | 232.5 ± 20.5 | 11.6 ± 1.3 | 5.0 ± 0.3 |

All values are given as means ± SD.

The percentage of GH cells per unit volume ($mm^3$) of total pituitary gland tissue, i.e. the volume density, was also significantly reduced by neonataly applied SRIH-14 (Fig. 2c). The most prominent decrease in volume density of GH cells was observed when examined immediately after treatment (by 67.6%; $p<0.05$). In the juvenile, peripubertal and adult periods of life, the percentages of

GH cells were reduced by 22.0%, 25.8% and 26.1%, respectively, compared to corresponding controls.

Neonatal SRIH-14 treatment did not induce any significant changes in body weight, absolute or relative pituitary weights in female rats at any age group (Table 1).

## DISCUSSION

The results of this study demonstrated that neonataly applied SRIH-14 had immediate and prolonged inhibitory effects on pituitary GH cells. The most prominent inhibitory effect was noticed immediately after SRIH-14 treatment, in the neonatal period of life.

Circulating GH levels are elevated in neonatal rats (Rieutort, 1974). Several *in vivo* and *in vitro* studies indicated that the reason is low responsiveness of neonatal pituitary to somatostatin, due to low numbers of its receptors (Khorram *et al.,* 1983; Rieutort, 1981; Cuttler *et al*., 1986). However, Reed *et al*. (1999) reported that the neonatal rat pituitary expresses the same complement of somatostatin receptors (sstr 1-5) as the adult pituitary. The same authors found that the expression of sst2 mRNA was age dependent. Levels of sst2 mRNA were low in pituitaries 2-day-old animals, but thereafter rose progressively until adulthood. However, pituitaries of neonatal animals expressed sst1, sst3, sst4, and sst5 mRNA with no significant ontogenic changes in expression of these subtypes. SRIH-14, used in our study, is known to bind to all five somatostatin receptors with high affinity (Patel, 1999), and therefore had the opportunity to directly affect GH cells in the neonatal period of life.

The possibility of indirect influence of SRIH on GH cells, through the inhibition of hypothalamic GHRH, should be taken into consideration. Thoss *et al*. (1995) demonstrated the expression of sstr 1, 3, 4, and 5 in the arcuate hypothalamic nucleus of 5 day old rats. Cella *et al*. (1990) reported a significant (about 40%) reduction in GH cell percentage in the pituitaries of neonatal rats after passive immunization against endogenous GHRH. However, they also reported a significant recovery 30 and 60 days after treatment.

In the pituitaries of control female rats, GH cell number per unit area slightly descended from the neonatal period of life up to adulthood, due to the growing blood vessels and connective tissue in the pituitaries. The volume of GH cells, on the other hand, increased with age, which resulted in the increase of the percentage of GH cells in the pituitary. The most prominent increase was noted from the peripubertal up to the adult period of life. Takahashi (1991) also reported the increase of GH cell percentage in the pituitaries of female rats from 30 to 60 days of age, when the growth rate was increasing (Chowen *et al*., 1993). In our experimental conditions, in SRIH-14 treated females, this increase of GH cell volume was not observed. On the contrary, the GH cell volumes at all age groups were similar to the ones found in the pituitaries of treated females examined neonataly. Therefore, comparing to the corresponding control, the most prominent decrease of GH cell volume was noted in the adult period of life. However, an attempt of normalization of the percentage of GH cells in time was

observed. Namely, a significant increase in number of GH cells per unit area in adult females neonataly treated with SRIH-14 was noted. When compared to the corresponding controls, this parameter increased about 25%. Combined with a 50% decrease in GH cell volume, it resulted in about 25% decrease in the percentage of GH cells in the pituitary.

The pituitary responds to physiological demands by modifying hormone synthetic and secretory activity, and by altering the relative proportions of different cellular subtypes that it contains (Nolan *et al*., 2004). Formation of new hormone-producing cells involves mitosis of differentiated cells, and maturation of undifferentiated cells. It has been shown that adult mice pituitary contains stem/progenitor cells that may function as "source" cells for new hormone-producing cells (Chen *et al*., 2005). In addition, Taniguchi *et al*. (2002) reported that about 10% of all proliferating cells in the pituitary are already differentiated cells. This percentage for GH cells is 30-40% at most, suggesting a very active production.

Neonatal SRIH-14 treatment did not affect body weight, absolute or relative pituitary weights in any examined age groups. In rats and mice the critical period of GH effect on weight begins in the second postnatal week (Rodier *et al*., 1990). GH cells of neonataly treated peripubertal and adult females were smaller, but their cytoplasm was weakly immunostained suggesting increased hormone secretion. Combined with a significant increase of GH cell number in the adult period, it can be assumed that circulating GH levels were not reduced when compared to the corresponding controls.

On the basis of our results we can conclude that neonatal application of SRIH-14 to neonatal female rats exerts a significant immediate and prolonged inhibitory effect on GH cells, but does not affect the growth rate from neonatal period of life up to adulthood.

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## NEONATALNO APLIKOVAN SOMATOSTATIN IMA NEPOSREDAN I ODLOŽEN INHIBITORNI UTICAJ NA GH ĆELIJE HIPOFIZE

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SADRŽAJ

Ispitivan je neposredan i odložen efekat neonatalnog tretmana somatostatinom (SRIH-14) na somatotropne (GH) ćelije. Ženke pacova su dva puta dnevno s.c. tretirane sa 20 μg SRIH-14/100g t.m. u toku pet dana (od 3. do 7. dana života) i žrtvovane u različitim periodima života: u neonatalnom (8. dan), juvenilnom (16. dan), peripubertalnom (38. dan) i adultnom (80. dan) periodu. GH ćelije su imunocitohemijski obeležene metodom peroksidaza-antiperoksidaza a morfometrijskim i stereološkim metodama određivani su broj GH ćelija po jedinici površine, njihov volumen i volumenska gustina. Nakon somatostatinskog tretmana, najznačajnije smanjenje svih merenih parametara utvrđeno je u neonatalnom periodu. SRIH-14 je izazvao značajno smanjenje volumena i volumenske gustine GH ćelija u juvenilnom, peripubertalnom i adultnom periodu života. Broj GH-pozitivnih ćelija po $mm^2$ je bio značajno smanjen kada je ispitivan neposredno nakon tretmana, ali je bio značajno povećan kod adultnih ženki. Telesna masa, kao i apsolutne i realtivne mase hipofiza nisu bile izmenjene ni u jednoj od ispitivanih starosnih grupa. Dobijeni rezultati ukazuju da neonatalni tretman somatostatinom izaziva značajan neposredan i odložen inhibitoran uticaj na GH ćelije, ali ne utiče na stopu rasta kod ženki pacova.