

# Effects of salsolinol and its antagonistic analogue, 1-MeDIQ, on growth hormone release in nursing sheep

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Suckling induces a GH surge simultaneously to that of prolactin, so we tested whether salsolinol, a dopamine derivative (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline), participates in the regulatory process of GH secretion in lactating sheep. A series of intracerebroventricular (i.c.v.) infusions of salsolinol, in two doses, was performed in nursing sheep, without suckling, during the fifth week of lactation. In other suckling sheep, we infused i.c.v. a structural analogue of salsolinol—1-methyl-3,4-dihydroisoquinoline (1-MeDIQ), which is able to antagonize salsolinol's action. Intracerebroventricular treatment of nursing sheep with a lower dose of salsolinol (total 50 ng) significantly increased plasma GH concentration, as compared with the concentrations noted before the infusion and in nursing controls. A higher dose of salsolinol (total 5 µg) did not affect GH release significantly. Intracerebroventricular treatment with 1-MeDIQ (total 300 µg) significantly reduced basal GH release, not affecting a pattern of GH surge in response to suckling. In conclusion, salsolinol may affect the regulatory process of GH secretion in lactating sheep, but its role seems not to be major.

Key words: salsolinol, 1-MeDIQ, growth hormone, lactation, nursing sheep

## INTRODUCTION

Prolactin and growth hormone (GH) are the primary pituitary hormones responsible for the proper process of lactation (Tucker 2000, Kelly et al. 2002, Trott et al. 2008). They induce mammary gland development (mammatogenesis) and then milk synthesis (lactogenesis) and secretion (galactopoiesis). During lactation, the maternal plasma concentrations of prolactin and GH increase and the suckling stimulus cause a rapid and transient surge of these hormones from the pituitary gland (Wehrenberg and Gaillard 1989, Misztal et al. 2008). Grosvenor and coauthors (1968) demonstrated, that the suckling stimulus induces a depletion of pituitary content of GH in lactating rats, so an increase in plasma GH levels may be due to signal(s) that increase GH secretion, but do not act at the transcriptional level. Proper neuroendocrine mechanisms

responsible for the maintenance of increased prolactin and GH secretion as well as induction of their surges have been extensively studied (Riskind et al. 1984, Arbogast and Voogt 1996, Escalada et al. 1997, Anderson et al. 2006, Misztal et al. 2008, 2010). Endogenous opioid peptides and hypothalamic growth hormone-releasing hormone (GHRH) has been suggested to have a role in the control of GH secretion during suckling (Riskind et al. 1984, Wehrenberg and Gaillard 1989, McMahon et al. 2001a,b).

In the last decade, attention was paid to salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline), a dopamine-derived catecholaminic compound (Naoi et al. 2002), which is well-known for its involvement in the progression of a disease characterized by dysfunctional dopaminergic neurons (Moser et al. 1995, Antkiewicz-Michaluk 2002). It has been shown to stimulate prolactin release in rodents (Toth et al. 2001, 2002) and ruminants (Hashizume 2008, 2009) under different physiological conditions. Recently, our group has found salsolinol in the mediobasal hypothalamus (MBH) of lactating sheep and an increase in the extra-

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cellular concentration of this compound in response to suckling (Misztal et al. 2008). We have also shown that exogenous salsolinol stimulates pituitary prolactin release in lactating sheep, following infusion into the third ventricle (IIIv) of the brain (Gorski et al. 2009).

Only one structural analogue of salsolinol, 1-methyl-3,4-dihydroisoquinoline (1MeDIQ), is known to antagonize some of its endogenous actions (Bodnar et al. 2004a, Mravec et al. 2004). 1-MeDIQ was proven to be a very potent inhibitor of salsolinol-induced prolactin release and completely blocked prolactin response to suckling and immobilization stress in lactating female rats (Bodnar et al. 2004a). Moreover, 1-MeDIQ was also able to block the secretory response of prolactin induced by formalin stress (Bodnar et al. 2004a). Our recent report showed that in farm animals such as sheep, 1-MeDIQ is able to inhibit basal prolactin release in nursing ewes and reduce suckling-induced prolactin surge, acting at the central nervous system (CNS) level (Misztal et al. 2010).

To study the participation of salsolinol in the neural stimulatory mechanism of GH release in nursing sheep, we tested the GH response to both salsolinol and 1-MeDIQ, following the infusion into the IIIv. We assumed that salsolinol was able to enhance GH release in nursing sheep and 1-MeDIQ would diminish basal GH release and/or reduce GH surge induced by suckling.

## METHODS

### Animals, management and brain surgery

All animal procedures were conducted in accordance with the Polish Guide for the Care and Use of Animals (1997) and approved by the Local Ethics Committee.

Two experiments were performed on nursing sheep (3- to 4-year-old, Polish longwool, 50–55 kg b.w.) during two breeding seasons to test the effects of salsolinol ( $n=12$ ) and 1-MeDIQ ( $n=7$ ) on GH secretion. Ewes were mated naturally in September and lambled in the following February. They were maintained indoors in individual pens under natural lighting conditions (52°N, 21°E). The animals were fed twice daily with a diet formulated to fulfill all of the National Research Institute of Animal Production's recommendations for pregnancy and lactation (NRIAP 1993) with water available *ad libitum*.

All ewes were implanted with a stainless steel guide cannulae (1.4 mm o.d.) into the IIIv during the second month of pregnancy. The implantation was performed under general anaesthesia, through a drill hole in the skull, in accordance with the stereotaxic co-ordinate system for sheep hypothalamus (Welento et al. 1969) and a procedure described by Traczyk and Przekop (1963), positions: frontal, 31 mm and sagittal, 0.5 mm. The guide cannulae were fixed to the skull with stainless steel screws and dental cement. The external opening to the canal was closed with a stainless steel cap.

### Experimental design

#### Experiment 1 – effect of exogenous salsolinol on GH release

Salsolinol (Sigma) was dissolved in Ringer-Locke solution (RLs), divided into portions and stored at  $-20^{\circ}\text{C}$ . The experiment was performed during the fifth week of lactation, between days 28 and 32 after parturition, when a clear surges of the lactogenic hormones, prolactin and GH, were observed during suckling (Misztal et al. 2008). The ewes were randomly divided into groups and infused intracerebroventricularly (i.c.v.) with: (1) lower (total 50 ng,  $n=6$ ) or (2) higher (total 5  $\mu\text{g}$ ,  $n=6$ ) dose of salsolinol. The doses of salsolinol were selected according to our previous study (Gorski et al. 2009), in which they elicited changes in the secretion of prolactin in nursing sheep. Three to four days before or after salsolinol treatment, the selected ewes ( $n=6$ ) were infused with RLs as the control. The treatments were performed in a series of five 10-min infusions,  $5 \times 10 \text{ ng}/20 \mu\text{l}/10 \text{ min}$  (lower dose) or  $5 \times 1 \mu\text{g}/20 \mu\text{l}/10 \text{ min}$  (higher dose), at 20-min intervals. A new portion of salsolinol was used each time to keep the molecule stable during the experiment. All infusions were performed from 12:30 PM to 03:00 PM, using a BAS Bee™ microinjection pump (Bioanalytical Systems Inc., West Lafayette, IN, USA) and calibrated 1.0-ml gas-tight syringes. The pre-infusion period was from 10:00 AM to 12:30 PM.

During the experiment, nursing sheep were kept together with their lamb(s) in comfortable cages where they could lie down. Lamb(s) had restrained access to the mother's udder from 11:00 AM to 03:00 PM, but remained in visual and tactile contact in front of the mother. Blood samples were collected from lactating

ewes from 10:00 AM to 03:00 PM, at 10-minute intervals through a catheter inserted into the jugular vein a day before the experiment. The blood volume taken each time was about 4 ml per sample (total about 120 ml). After centrifugation in heparinized tubes, plasma was stored at  $-20^{\circ}\text{C}$  until GH was assayed.

#### Experiment 2 – effect of 1-MeDIQ on basal GH release and suckling-induced surge

1-MeDIQ was synthesized and kindly provided by Prof. Ferenc Fülöp from the Institute of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Szeged, Hungary. It was dissolved in RLs, divided into portions and stored at  $-20^{\circ}\text{C}$ . The experiment was performed during the fifth week of lactation, between days 28 and 32 after parturition. All ewes ( $n=7$ ) were infused i.c.v. twice with 1-MeDIQ or RLs alone (control) in a series of five 30-min infusions,  $5 \times 60 \mu\text{g}/60 \mu\text{l}/30 \text{ min}$  (total  $300 \mu\text{g}$ ), at 30-min intervals. The dose of 1-MeDIQ was selected according to our previous study (Misztal et al. 2010), in which it elicited changes in the secretion of prolactin in nursing sheep. The infusions were done from 10:00 AM to 03:00 PM, using a BAS Bee™ micro-injection pump and calibrated 1.0-ml gas-tight syringes. A new portion of 1-MeDIQ was used each time to keep the stability of the molecule during the experiment.

During the experiment, nursing sheep were kept together with their lamb(s) in comfortable cages, where they could lie down and had unrestrained access to hay. Lamb(s) had restrained access to the mother's udder from 09:00 AM to 12:30 PM, having visual and tactile contact in front of the mother. After this time, lamb(s) were allowed to suck the mother's milk. The suckling was then monitored to the end of the experiment. Simultaneously, blood samples were collected from 10:00 AM to 03:00 PM at 10-min intervals, as described above. After centrifugation in heparinized tubes, plasma was stored at  $-20^{\circ}\text{C}$  until GH was assayed.

#### Analytical techniques

The concentration of GH in plasma was assayed by the RIA double-antibody method, using antbovine GH and antirabbit  $\gamma$ -globulin antisera and bovine GH standard (NIDDK-GH-B-1003A). The full characteristics of the antiserum and method were described by

Dvorak and colleagues (1978). The assay sensitivity for growth hormone was  $0.6 \text{ ng/ml}$ , and the intra- and inter-assay coefficients of variation were 5.9 and 10.2%, respectively.

#### Statistics

The effect of the salsolinol and 1-MeDIQ treatments on the plasma GH concentration was examined by one-way analysis of variance (ANOVA, Statistica, StatSoft, Inc., Tulsa, OK, USA). The Tukey *post-hoc* test was used for the comparison of plasma GH concentrations between groups either during the pre- and infusion periods (Experiment 1) or during the non-suckling and suckling periods (Experiment 2). The same test was also used for the comparison of GH concentrations between the 30-min periods of the experiment within the control and 1-MeDIQ-infused group (Experiment 2). All data are expressed as means  $\pm$  SEM.

## RESULTS

#### Experiment 1 – effect of exogenous salsolinol on GH release

The mean plasma GH concentration before and during the period of control infusion was  $4.89 \pm 0.18$  and  $4.58 \pm 0.18 \text{ ng/ml}$  (Fig. 1), respectively. In ewes treated with the lower dose of salsolinol, plasma GH concentration before infusion was  $5.22 \pm 0.20 \text{ ng/ml}$  and

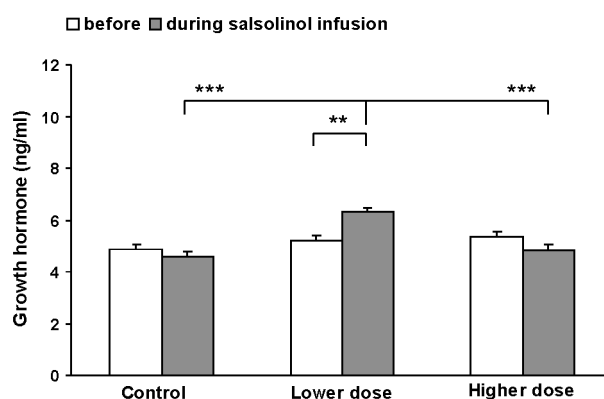


Fig. 1. Mean plasma growth hormone concentration in nursing sheep infused with Ringer-Locke solution (control), the lower ( $5 \times 10 \text{ ng}/20 \mu\text{l}/10 \text{ min}$ ) and higher ( $5 \times 1 \mu\text{g}/20 \mu\text{l}/10 \text{ min}$ ) dose of salsolinol. Pre-infusion period 10:00 AM–12:30 PM (white bars); infusion period 12:30 PM–03:00 PM (grey bars). \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .

increased significantly in response to this compound to  $6.29 \pm 0.20$  ng/ml ( $P < 0.01$ ). This concentration was also significantly ( $P < 0.001$ ) higher than the respective plasma GH level noted in control ewes. In ewes treated with the higher dose of salsolinol, plasma GH concentration before infusion was  $5.33 \pm 0.18$  ng/ml and did not change significantly in response to this compound,  $4.84 \pm 0.19$  ng/ml. Plasma GH concentration during the infusion of the higher dose of salsolinol was significantly lower ( $P < 0.001$ ) than the respective concentration during the infusion of the lower dose. Figure 2 shows the mean concentrations of GH in consecutive blood samples in the control, low and high dose of salsolinol-infused sheep.

### Experiment 2 – effect of 1-MeDIQ on basal GH release and suckling-induced surge

In ewes treated with control infusion, the mean plasma GH concentration during the non-suckling period was  $7.58 \pm 0.66$  ng/ml and increased significantly ( $P < 0.001$ ) during the suckling period to  $13.20 \pm 0.68$  ng/ml (Fig. 3). The distribution of mean plasma GH concentrations in 30-min periods in these ewes showed that the concentration increased significantly ( $P < 0.001$ ) during the first 10–30 min of suckling ( $20.32 \pm 1.45$  ng/ml) and maintained a significantly ( $P < 0.05$ ) high level through the next 30 min. ( $14.48 \pm 1.45$  ng/ml), as compared to the concentrations noted

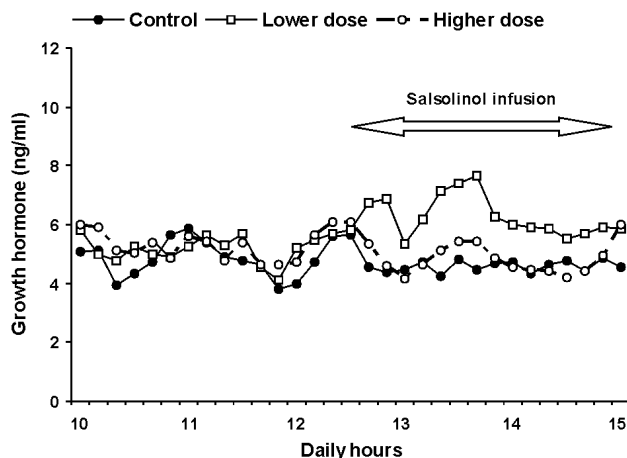


Fig. 2. Mean plasma growth hormone concentrations in consecutive blood samples collected from nursing sheep infused with: Ringer-Locke solution (control); the lower ( $5 \times 10$  ng/20  $\mu$ l/10 min) and the higher ( $5 \times 1$   $\mu$ g/20  $\mu$ l/10 min) dose of salsolinol. Infusion period 12:30 PM–03:00 PM (white arrow). SEM is omitted.

during the consecutive 30-min periods before suckling (from  $6.67 \pm 1.45$  to  $9.02 \pm 1.45$  ng/ml). A similar pattern of GH release occurred in ewes treated with 1-MeDIQ:  $4.96 \pm 0.66$  vs.  $9.60 \pm 0.68$  ng/ml ( $P < 0.001$ , Fig. 3), during the non-suckling and suckling period, respectively. However, these concentrations were significantly ( $P < 0.05$ – $P < 0.01$ ) lower than the respective plasma GH levels noted in the control. The distribution of mean plasma GH concentrations in 30-min periods in 1-MeDIQ-treated ewes showed a clear GH surge in response to suckling ( $14.84 \pm 1.45$  ng/ml), as compared to the concentrations noted during the consecutive 30-min periods before suckling (from  $4.08 \pm 1.26$  to  $5.64 \pm 1.45$  ng/ml,  $P < 0.01$ – $P < 0.001$ ). Figure 4 shows the mean concentrations of GH in consecutive blood samples in the control and 1-MeDIQ-infused sheep.

### DISCUSSION

The presented results suggest that salsolinol, a derivative of DA, may at least partially affect the secretory activity of the somatotrophic axis in sheep during lactation. Specifically, a low dose of salsolinol was able to stimulate GH release in nursing sheep, following infusion into the CNS. Moreover, the i.c.v. treatment of such sheep with 1-MeDIQ, an antagonizing analogue of salsolinol, inhibited basal GH release, not disturbing the GH surge induced by suckling.

It has been previously demonstrated that salsolinol

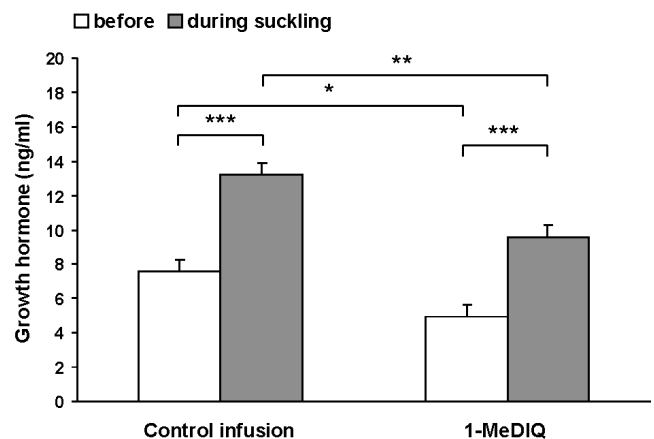


Fig. 3. Mean plasma growth hormone concentration in nursing sheep infused with Ringer-Locke solution (control) and 1-MeDIQ ( $5 \times 60$   $\mu$ g/60  $\mu$ l/30 min). Non-suckling period 10:00 AM–12:30 PM (white bars); suckling period 12:30 PM–03:00 PM (grey bars). \*  $P < 0.05$ ; \*\*  $P < 0.01$ ; \*\*\*  $P < 0.001$ .



is present in the MBH of lactating sheep (Misztal et al. 2008) and that it may participate in the neuroendocrine mechanism responsible for both maintaining increased secretion of prolactin and generating prolactin surge induced by suckling (Górski et al. 2009, Misztal et al. 2010). Here, we showed that this DA derivative increased plasma GH concentration in nursing sheep; surprisingly the effective dose of salsolinol was less than in case of prolactin (Górski et al. 2009). This might result from a different way of salsolinol action on both hormones. The molecular structure of the salsolinol receptor has not been determined but Homiesko and coworkers (2003) demonstrated that salsolinol binding sites are located in both the anterior pituitary (AP) and CNS. The *in vitro* study showed that salsolinol stimulates prolactin release from the rat and bovine AP lactotropes, proving the existence of salsolinol receptors in the pituitary cells (Toth et al. 2001, Hashizume et al. 2008). Moreover, Radnai and others (2005) demonstrated that a cAMP-coupled mechanism is probably involved in the prolactin-releasing action of salsolinol at the level of lactotropes. On the other hand, salsolinol and its derivatives were shown to induce the alteration of protein synthesis in the neural cells (Kheradpezhrouh et al. 2003). Thus, the lower dose of salsolinol infused i.c.v. could affect primarily the neurons, which are directly related with GH secretion, that is: GHRH neurons and/or somatostatin (SRIF) neurons or other neurons,

affecting the GHRH and SRIF release. In turn, the higher dose could make the supersaturation of salsolinol receptors, located in the CNS, without inducing the clear GH response.

It is generally accepted that GH synthesis and release from the pituitary somatotropes is primarily controlled by the opposing actions of the hypothalamic neuropeptides GHRH and SRIF (Tannenbaum and Ling 1984, Plotsky and Vale 1985). The GHRH neurons are localized to the arcuate nucleus and the SRIF neurons are found in the periventricular nucleus (McMahon et al. 2001a). These neuroendocrine cells project to the external zone of the median eminence (ME) and the peptides are secreted into the hypophyseal portal circulation to act upon the pituitary somatotropes. It is noteworthy that the tip of the infusing cannula was placed directly behind the ME, allowing passage of the infused compounds through the cerebrospinal fluid of the third ventricle to the neighbouring target cells (Skipor and Thiery 2008). Up to now, there is no data indicating that neurons producing GHRH and SRIF are receptive to salsolinol. Many other neuroendocrine factors can also regulate the secretion of GH in mammals *via* altering release of GHRH and/or SRIF, communicating between GHRH and SRIF neurons, or acting independently at the AP somatotropes (McMahon et al. 2001a). Earlier studies in sheep and other species with adrenergic receptor agonists and antagonists have emphasized the role of the noradrenergic system in the regulation of GH secretion (Tsagarakis et al. 1989, Malozowski et al. 1990, McMahon et al. 2001a,b). Noradrenaline (NA) stimulates the release of GHRH at both  $\alpha(1)$  and  $\alpha(2)$ -adrenoceptors and reduces the activity of SRIF neurons (Tsagarakis et al. 1989, McMahon et al. 2001a,b). More recently, Iqbal and coauthors (2005) have provided evidence that noradrenergic regulation of GH in the sheep could involve direct modulation of GHRH and SRIF cells by the noradrenergic systems of the brain stem. Data received on rats during recent years showed that salsolinol did modulate NA release, however it concerned mainly the peripheral NA concentration. Salsolinol was shown to be a very potent inhibitor of immobilization stress-induced NA release (Bodnar et al. 2004b). It also decreased tissue DA level and increased NA/DA ratio indicating a possible decrease of NA release (Szekacs et al. 2007a,b). The above inhibitory properties of salsolinol with respect to NA may however contradict the hypothetical stimu-

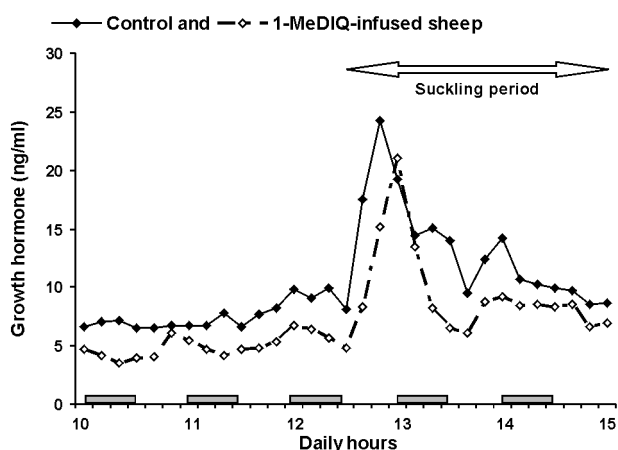


Fig. 4. Mean plasma growth hormone concentrations in consecutive blood samples collected from nursing sheep infused with: Ringer-Locke solution (control) and 1-MeDIQ ( $5 \times 60 \mu\text{g}/60 \mu\text{l}/30 \text{ min}$ ). Infusion periods (grey bars); suckling period 12:30 PM–03:00 PM (white arrow). SEM is omitted.

latory pathway: salsolinol-NA-GHRH in nursing sheep. On the other hand, the central action of salsolinol might be in keeping with the action of the endogenous opioid peptides, which are able to stimulate GH release through a GHRH dependent and GHRH independent pathway (Wehrenberg et al. 1985, Armstrong et al. 1990). More studies are needed to recognize the interactions between these compounds at the CNS level in lactating females.

To support the participation of salsolinol in the neuroendocrine regulatory mechanism of GH release in nursing sheep, 1-MeDIQ have diminished basal GH secretion, following direct administration into the CNS. Mravec and others (2004) found that 1-MeDIQ is able to induce a massive increase in plasma NA level. Thus, our data suggest an exclusion of this catecholamine as a mediator of the salsolinol effect on GH release. Interestingly, 1-MeDIQ did not disturb the GH surge induced by suckling. A similar, rapid and transient increase in plasma GH concentration after the suckling stimulus and a return to baseline values by 30–60 min after the onset of suckling was observed in most of individuals from both the control and treated group. Usually, the substantial suckling was observed a few (at least two) times, each followed by an increase in plasma GH concentration, but the subsequent surges were lower than the first, elicited by hungry lambs. Our earlier study concerning prolactin secretion in nursing sheep (Misztal et al. 2010) showed that either the basal prolactin release during the non-suckling period or the prolactin surge induced by suckling was reduced, following similar i.c.v. treatment with 1-MeDIQ. Based on the distribution of mean plasma GH concentrations in the consecutive blood samples as well as in 30-min periods in control and 1-MeDIQ-treated sheep it seems that salsolinol is not a direct stimulator of GH surge during suckling. Studies on rats showed no significant changes in the secretion of the pituitary hormones in response to salsolinol and 1-MeDIQ, except of prolactin (Toth et al. 2001, Radnai et al. 2005).

## CONCLUSION

Basing on our data, concerning GH secretion in lactating sheep, we suggest that salsolinol may affect the regulatory process of GH secretion during lactation, but its role seems not to be major.

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