Domestic Animal Endocrinology 59 (2017) 75–80

Contents lists available at ScienceDirect

Domestic Animal Endocrinology

journal homepage: www.domesticanimalendo.com

Involvement of salsolinol in the suckling-induced oxytocin surge in sheep

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ARTICLE INFO

Article history:
Received 13 July 2016
Received in revised form 22 October 2016
Accepted 1 November 2016

Keywords:
Salsolinol
Oxytocin surge
Posterior pituitary
Suckling
Lactation

ABSTRACT

During lactation, the main surge of oxytocin is induced by a suckling stimulus. Previous studies have shown that salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline), a dopamine-derived compound, stimulates both the synthesis and the release of oxytocin in lactating sheep. The objective of the present study was to verify the hypothesis that salsolinol is involved in the mechanism that generates the oxytocin surge that occurs during suckling. Thus, a structural analogue of salsolinol, 1-methyl-3,4-dihydroisoquinoline (1MeDIQ), known to antagonize some of its actions, was infused into the third ventricle of the brain of lactating sheep nursing their offspring. Serial 30-min infusion of 1MeDIQ (4×60 μg/60 μL) or vehicle were administered at 30-min interval from 10 AM to 2 PM. The experimental period in every ewe consisted of a nonsuckling period (10 AM–12 PM) and a suckling period (12 PM–2 PM). Blood samples were collected every 10 min, to measure plasma oxytocin concentration by RIA. In control sheep, oxytocin surges of high amplitude were observed during the suckling period. The oxytocin surges induced by suckling were significantly ($P < 0.01$) diminished in sheep receiving 1MeDIQ infusions as compared to those that received control infusions. However, no significant effect of 1MeDIQ was observed on basal oxytocin release, before suckling. Furthermore, oxytocin release, as measured by the area under the hormone response curve (AUC), was significantly decreased by the administration of 1MeDIQ during the suckling period. This study shows that elimination of the effect of salsolinol within the central nervous system of lactating sheep attenuates the oxytocin surge induced by suckling. Therefore, salsolinol may be an important factor in the oxytocin-stimulating pathway in lactating mammals.

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1. Introduction

Oxytocin, a 9-amino acid neuropeptide, is primarily synthetized by magnocellular and parvocellular neurosecretory cells of the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei [1]. Within the magnocellular neurons, oxytocin bounded with its protein carrier, neurophysin I, is transported along axons, which terminals are located in the posterior pituitary [2]. Suckling increases the electrical activity of oxytocinergic neurons, which lead to pulsatile oxytocin surge from posterior pituitary to the peripheral circulation. Then, after oxytocin reaches mammary gland, it acts on myoepithelial cells of the alveoli, causing the movement of milk from the place of storage to the nipple [3,4].

During lactation, central oxytocin stimulation is necessary for enhanced synthesis and storage of the hormone in the hypothalamus and neurohypophysis, respectively. The

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0739-7240/$ – see front matter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.domaniend.2016.11.001

systemic secretion of oxytocin can be evoked by a number of neurotransmitters, where norepinephrine [5], histamine [6], and excitatory amino acids [7] have been directly implicated in the peripheral release of oxytocin in response to suckling. According to our recent studies, salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline), a product of hypothalamic dopaminergic neurons, has emerged as a potent factor stimulating oxytocin secretion during lactation [8]. Specifically, salsolinol, when administrated via intracerebroventricular (i.c.v.) infusion in lactating sheep, upregulated oxytocin gene expression in the PVN and SON, increased oxytocin peptide content in the posterior pituitary, and stimulated oxytocin release into the peripheral circulation. Notably, suckling increases extracellular salsolinol concentration in the infundibular nucleus/median eminence [9], and salsolinol has also been shown as a potential prolactin stimulating factor in such animals [10].

There was identified only one structural analogue of salsolinol—1-methyl-3,4-dihydroisoquinoline (1MeDIQ), which can antagonize some of its actions. We have shown that i.c.v. infusion of 1MeDIQ in lactating sheep reduces basal prolactin release and attenuates the suckling-induced prolactin surge [11]. Furthermore, treating lactating sheep with 1MeDIQ, under stress conditions, significantly diminished the salsolinol concentration and increased corticotrophin-releasing hormone within the infundibular nucleus/median eminence and cortisol concentrations in blood [12]. Using the antagonistic properties of 1MeDIQ, in the present study, we further investigated the role of salsolinol in the modulation of oxytocin secretion. The objective of this study was to verify the hypothesis that blockade of salsolinol action within the central nervous system would negatively affect the oxytocin surge induced by suckling in sheep nursing their offspring.

2. Materials and methods

2.1. Animal management

All experimental procedures were conducted in accordance with the Polish Guide for the Care and Use of Animals and were approved by the Local Ethics Committee. Ten mature Polish Longwool sheep (3–4 yr old) were mated naturally in September and lambed during the following February. They were maintained indoors in individual pens under natural lighting conditions (52°N, 21°E). The animals were fed twice a day with a diet formulated for pregnancy and lactation, in accordance with the recommendations of the National Research Institute of Animal Production (Norms, 1993), with hay and water available ad libitum. Sheep were well adapted to the experimental conditions and always had visual contact with neighboring sheep, even during the experimental period, to prevent stress due to social isolation.

2.2. Surgical procedure

During the third mo of pregnancy, each sheep was implanted with a stainless-steel guide cannula (1.4 mm OD) in the third ventricle of the brain. Animals were anesthetized with a mixture of xylazine (40 mg/kg), xylapan, and ketamine (10–20 mg/kg; all from Biowet, Pulawy, Poland) administered intravenously. The cannula was implanted through a hole drilled in the skull, according to the procedure described by Traczyk and Przekop [13], at coordinates 31-mm frontal and 0.5-mm sagittal using the stereotactic coordinate system for the sheep hypothalamus [14]. The guide cannula was fixed to the skull with stainless steel screws and dental cement (Villacryl S; Zhermapol, Warsaw, Poland). The external opening of the cannula was closed with a stainless steel cap. After surgery, sheep were injected daily with antibiotics for 5 d (1-g streptomycin and 1,200,000 IU benzylpenicillin; Polfa, Warsaw, Poland) and with analgesics for 4 d (50-mg sodium metamizole [Biovetalgin]; Biowet; or 1.5-mg meloxicam [Metacam]; Boehringer Ingelheim, Ingelheim am Rhein, Germany). Placement of the cannula in the third ventricle was confirmed by the outflow of cerebrospinal fluid during surgery and an injection of blue ink after euthanasia. The sheep used in the study were in good health conditions, showed normal behavior and food intake and had the correctly localized cannula.

2.3. Experimental design and drug treatment

1MeDIQ was synthesized and kindly provided by Prof. Ferenc Fülöp (Institute of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Szeged, Hungary). It was dissolved in Ringer–Locke solution (RL), then aliquoted and stored at −20°C. A new aliquot was used for each infusion to maintain the biological activity of the molecules during the experiment.

The experiment was performed on nursing sheep ($n = 10$) during the fifth week of lactation. 1MeDIQ or RL (vehicle—control) was delivered to the third ventricle in a series of four 30-min infusion (4×15 μg/60 μL each) at 30-min interval between 10 AM and 2 PM. The dosage was selected based on our previous studies [11,15]. The experiment consisted of a nonsuckling period from 10 AM to 12 PM and a suckling period from 12 PM to 2 PM. Lambs had no access to udder of mother from 9 AM, and stayed in front of her head with touch contact. The animals were used repeatedly in random order for each treatment (1MeDIQ vs control), and the experiments were carried out at 4-d interval. All infusions were delivered at a flow rate of 2 μL/min using a BAS Bee microinjection pump and calibrated 1.0-mL gas-tight syringes (Bioanalytical Systems Inc, West Lafayette, IN, USA). During the experimental procedures, sheep were kept together with theirs lambs in comfortable cages, where they could lie down and had unlimited access to hay.

One d before the experiment, each animal was equipped with a 16-gauge polyurethane catheter (Secalon Seldy; Becton Dickinson, Franklin Lakes, NJ) inserted into the jugular vein. To prevent clotting, the catheter was flushed with a sterile saline solution containing heparin (20 IU/mL). Before blood collection, approximately 5 mL of blood and heparin were aspirated and discarded. Serial blood samples (each 4 mL, 100 mL in total) were collected every 10 min. All blood samples were collected in prechilled tubes containing EDTA (50 μmol) and aprotinin (2.4 trypsin inhibitor

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