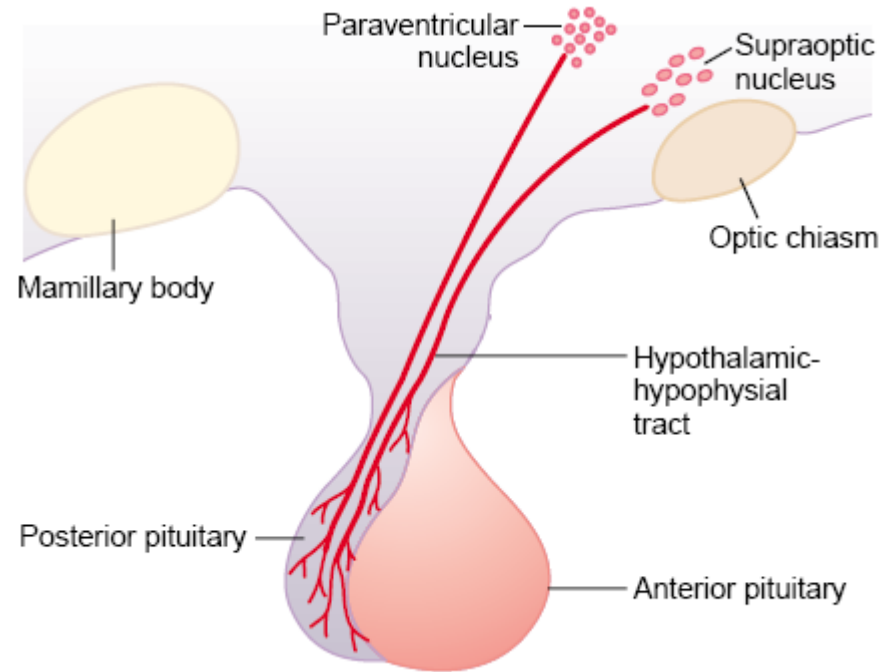


**LEPTIN AND GHRELIN DIFFERENTIALLY MODULATE  
NORADRENALINE RELEASE IN THE  
PARAVENTRICULAR NUCLEUS AND PLASMA  
OXYTOCIN LEVELS IN FEMALE RATS:  
A MICRODIALYSIS STUDY**

**Selim KUTLU, MD, PhD**

**Firat University, Faculty of Medicine,  
Department of Physiology, Elazig, TURKIYE**

## Introduction



► Oxytocin is also produced in some neurons of the parvocellular subdivision of the parvocellular PVN, which project to other brain regions such as the brain stem, medulla and cortex. Within the brain, oxytocin is known to act as a neuromodulator or neurotransmitter.

► It is well known that, noradrenergic afferents projecting from brainstem have stimulatory effects on the oxytocin secretion. Noradrenaline increases the firing rate of oxytocin cells.

► Additionally, noradrenaline causes inhibition of IPSP and augments EPSP in the magnocellular neurons.

- ▶ **Cholecystokinin administration induces oxytocin secretion. Systemic injection of CCK selectively increases the firing rate of oxytocin neurons.**
- ▶ **It is well established that CCK-induced excitation of oxytocin neurons is accompanied by increased NA release within the supraoptic and PVN.**
- ▶ **It has also been shown that CCK-induced excitation of oxytocin neurons can be prevented by an  $\alpha$ -adrenoreceptor antagonist.**
- ▶ **Thus, systemic administration of CCK has stimulatory effect on NA release in supraoptic and PVN.**

▶ Leptin is a peptide hormone, synthesized mainly in adipose tissue. Additionally, such as arcuate nucleus in hypothalamus, many tissues produce leptin.

▶ Reproductive system is a target for this hormone. It is known that leptin has an important role at the beginning of the puberty through stimulating gonadotropin secretion.

▶ Leptin's receptors have been detected in supraoptic and PVN.

- ▶ Ghrelin, an endogenous ligand of the GHS receptor, is mainly secreted from gastric endocrine cells. It exerts a strong stimulatory actions on growth hormone secretion and food intake.
- ▶ GHS receptors are expressed in various brain areas.
- ▶ Plasma ghrelin levels sharply increase at the end of pregnancy compared to those in non-pregnant rats. In line with this finding, administration of ghrelin into the lateral ventricle has been shown to activate oxytocin neurons in the PVN.

## **Aim:**

- ▶ **To investigate the effect of leptin on the CCK induced oxytocin secretion and NA concentration in PVN.**
- ▶ **Additionally, effects of ghrelin on oxytocin secretion and NA concentration in PVN were investigated in this study.**

# Materials and Methods

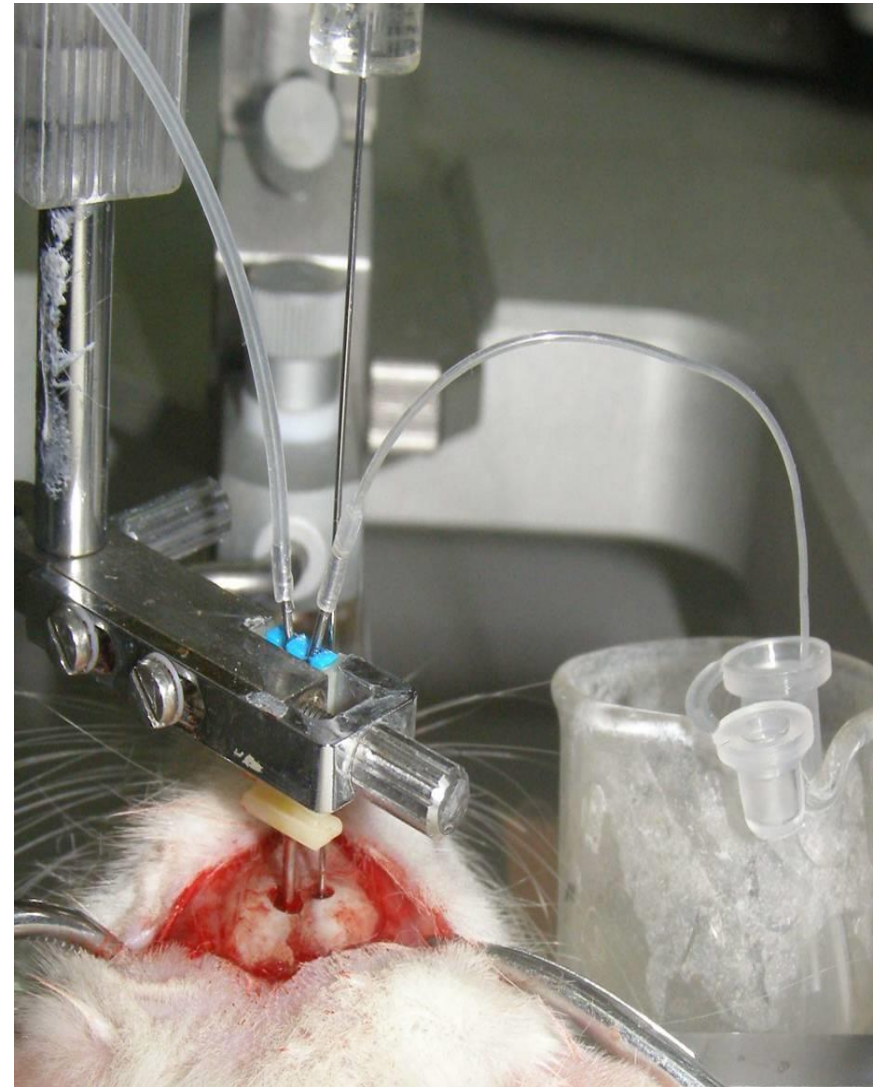
- ▶ Virgin female rats were anaesthetized with chloral hydrate.
- ▶ All animals were placed on a stereotaxic frame after carotid artery cannulation.





▶ A microdialysis guide cannula and probe were set into PVN with the guidance of the rat stereotaxic atlas, and artificial cerebrospinal fluid was run through a micropump throughout the experimental period.

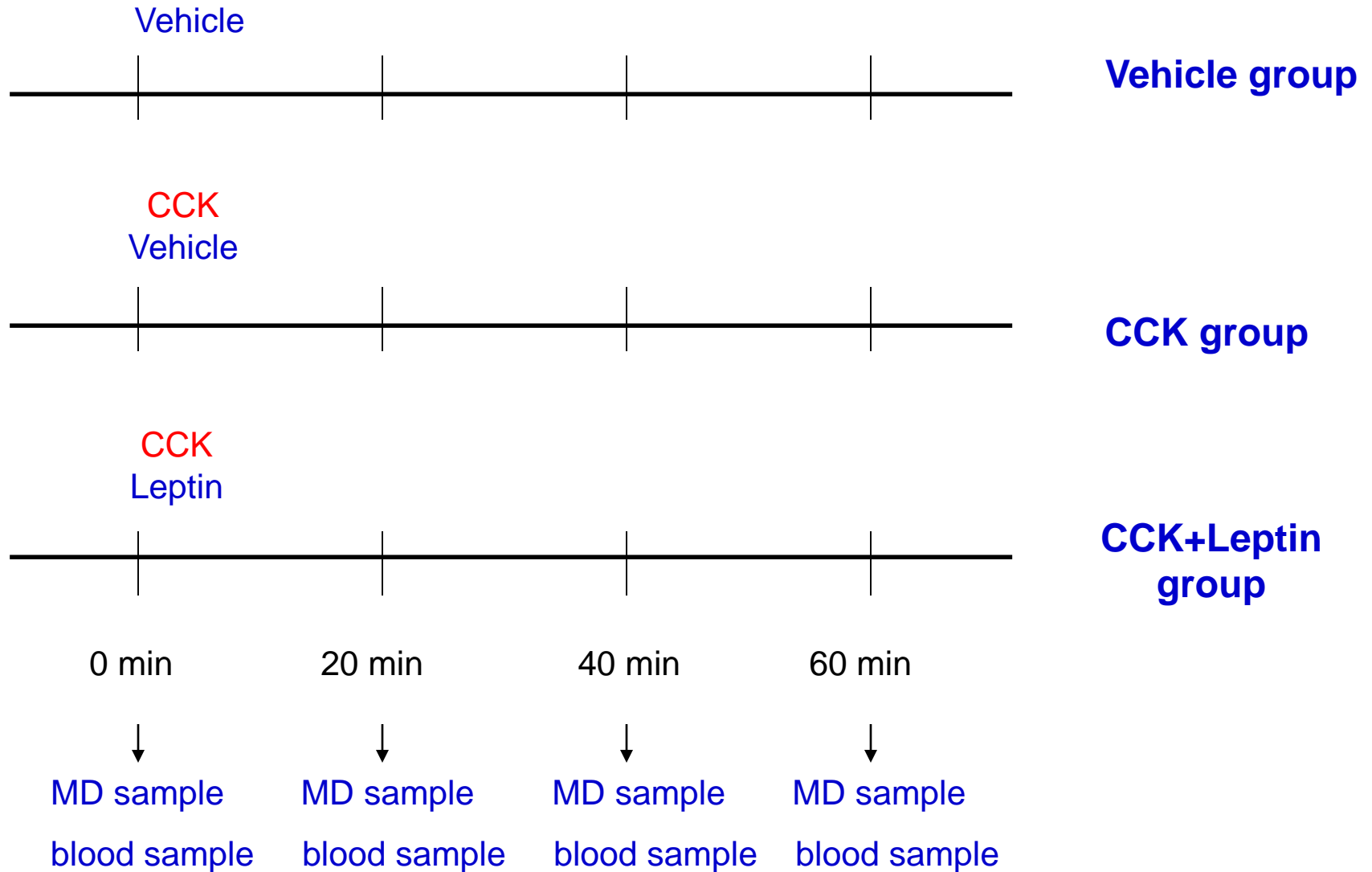
▶ One hour later, microdialysis samples were collected with 20 minutes intervals for 80 mins. At the same time, blood samples were obtained from carotid artery cannula.



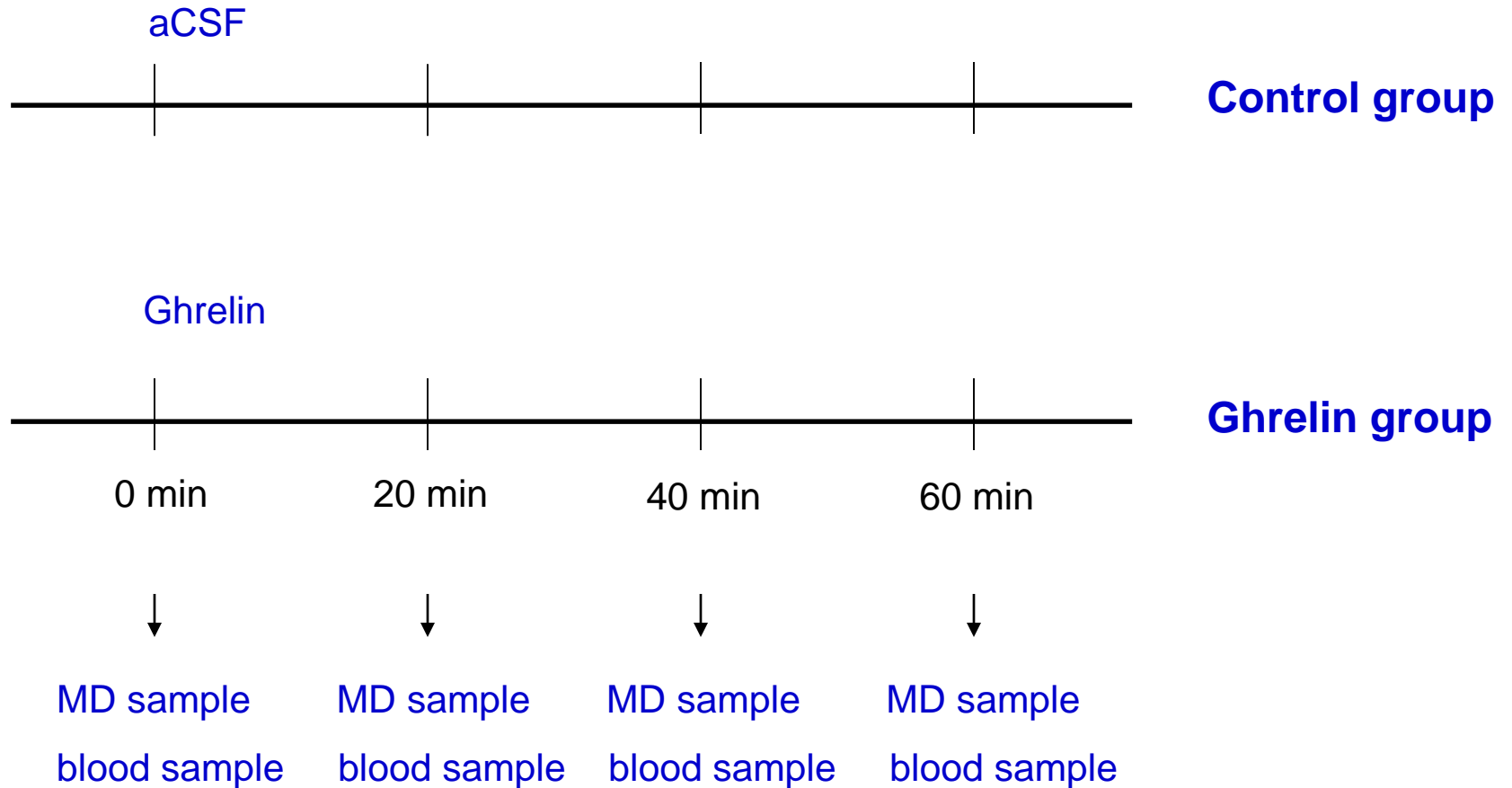


- ▶ After collection of the first sample, 50 $\mu$ g/kg CCK was intravenously administered to the CCK group.
- ▶ In addition to CCK, leptin (10 $\mu$ g/5 $\mu$ l) was ICV infused to the leptin group.
- ▶ The control and CCK groups received ICV vehicle infusion.

# Experiment 1



## Experiment 2



- ▶ **NA contents of samples were analyzed by HPLC-ECD system.**
- ▶ **NA levels were normalized by nominating the control level as 100%, and its levels in 20-mins samples were expressed as percentage of these values.**
- ▶ **Blood oxytocin levels were determined with RIA.**
- ▶ **Data were statistically analyzed by One-Way ANOVA.**

# Results

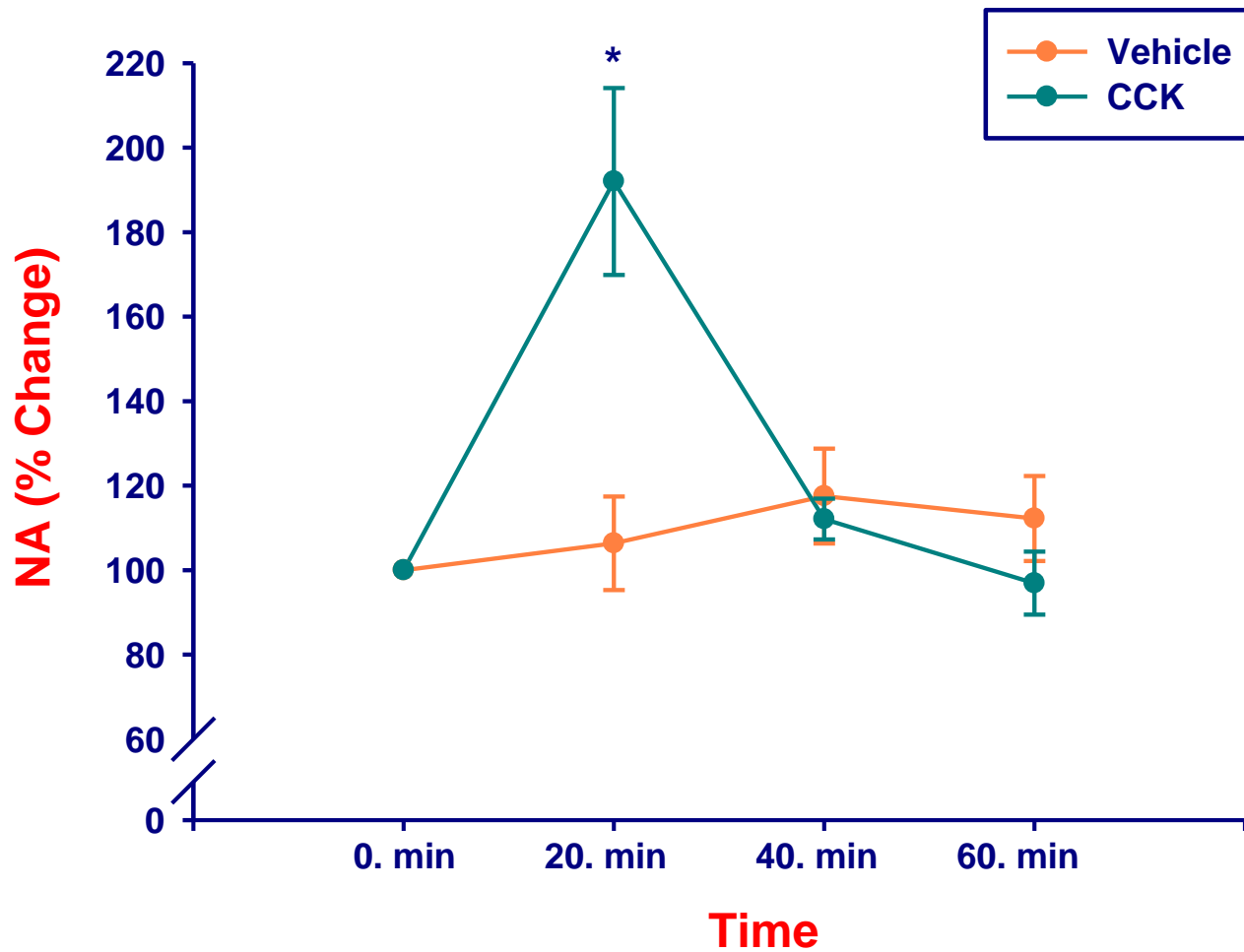


Fig 1: NA values of vehicle and CCK groups (Mean $\pm$ SEM). \*  $p < 0.001$



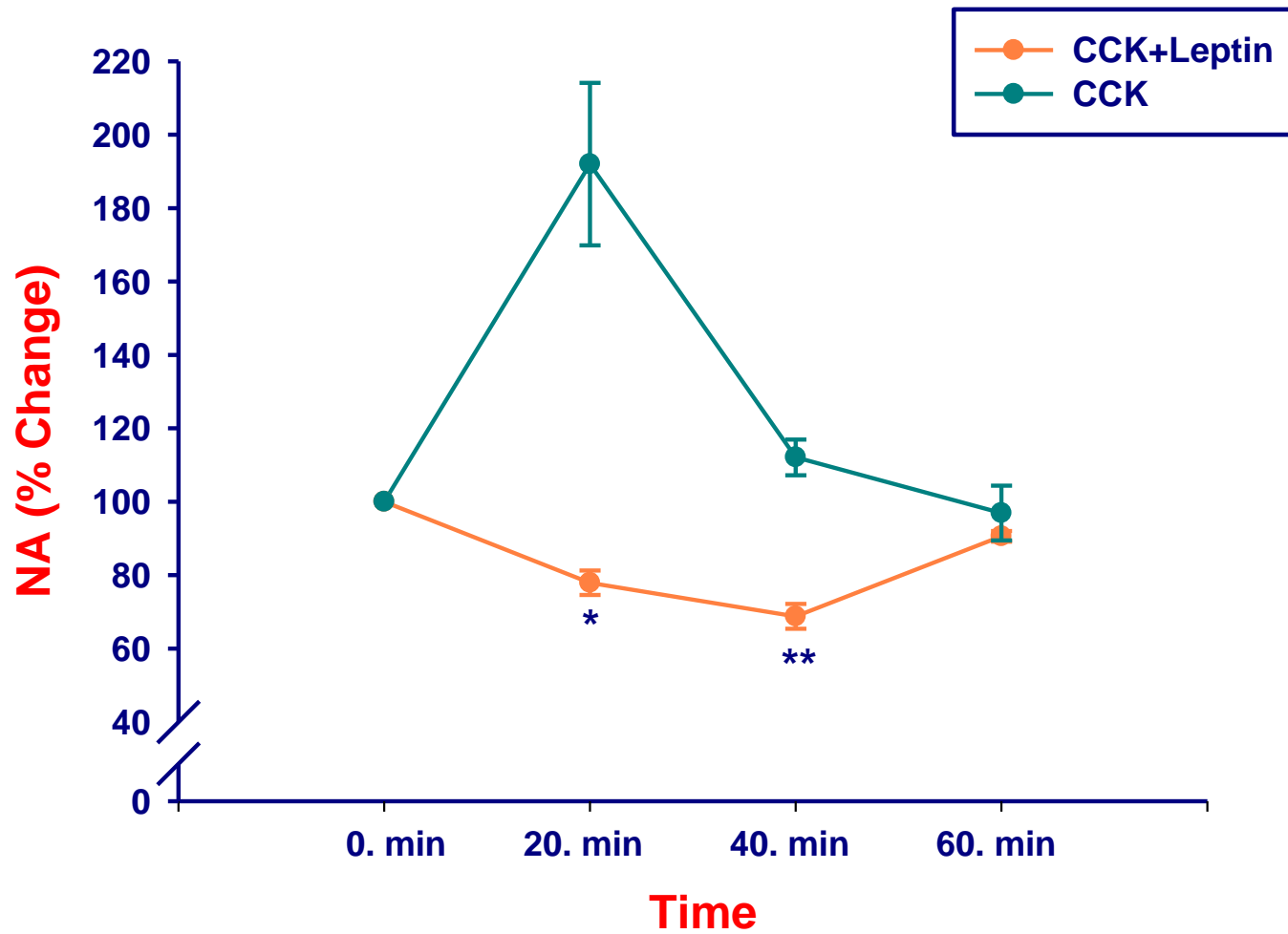


Fig 2. NA values of CCK and leptin groups (Mean $\pm$ SEM ).

\*  $p < 0.001$ , \*\*  $p < 0.01$

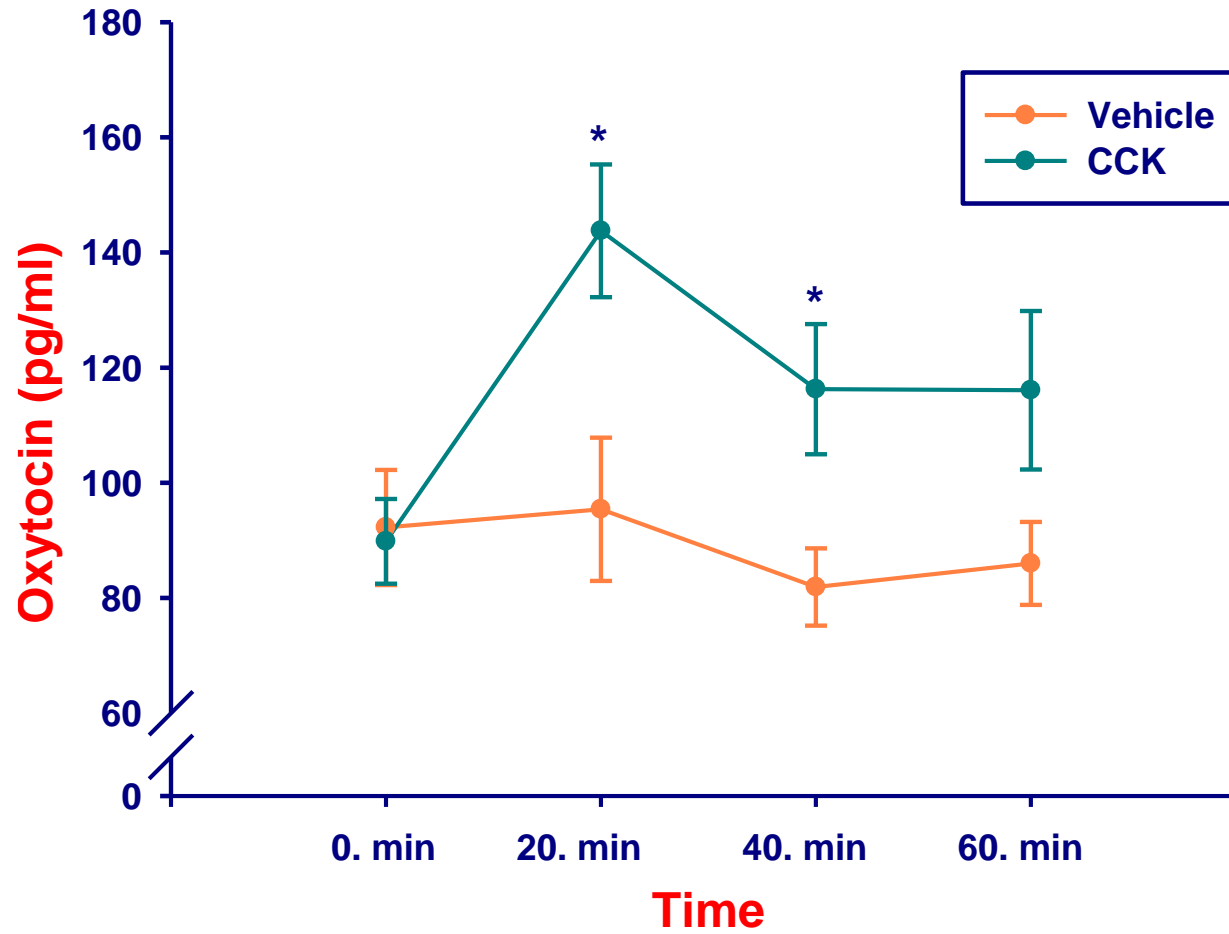


Fig 3. Oxytocin values of vehicle and CCK groups (Mean $\pm$ SEM). \*p<0.05.

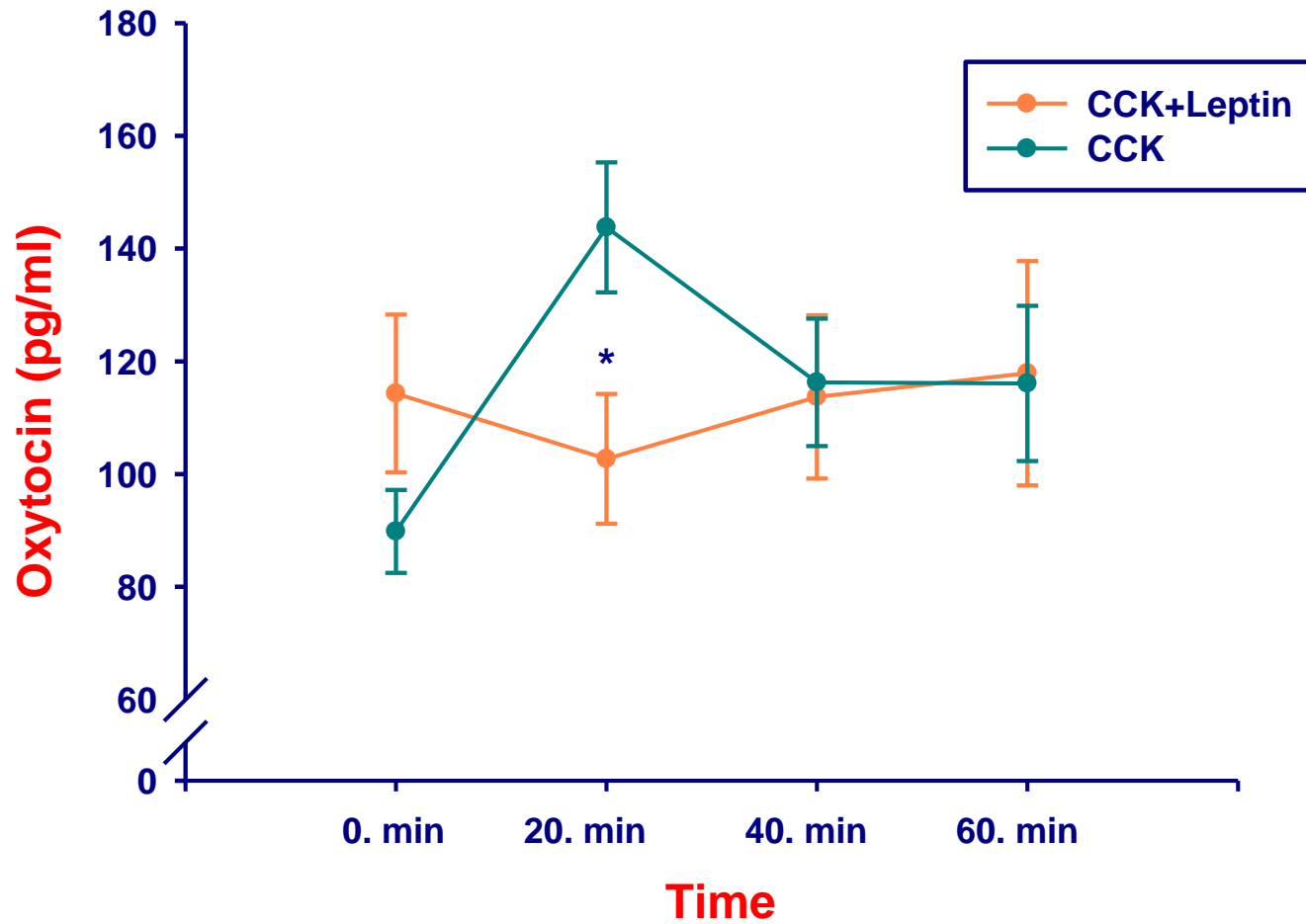
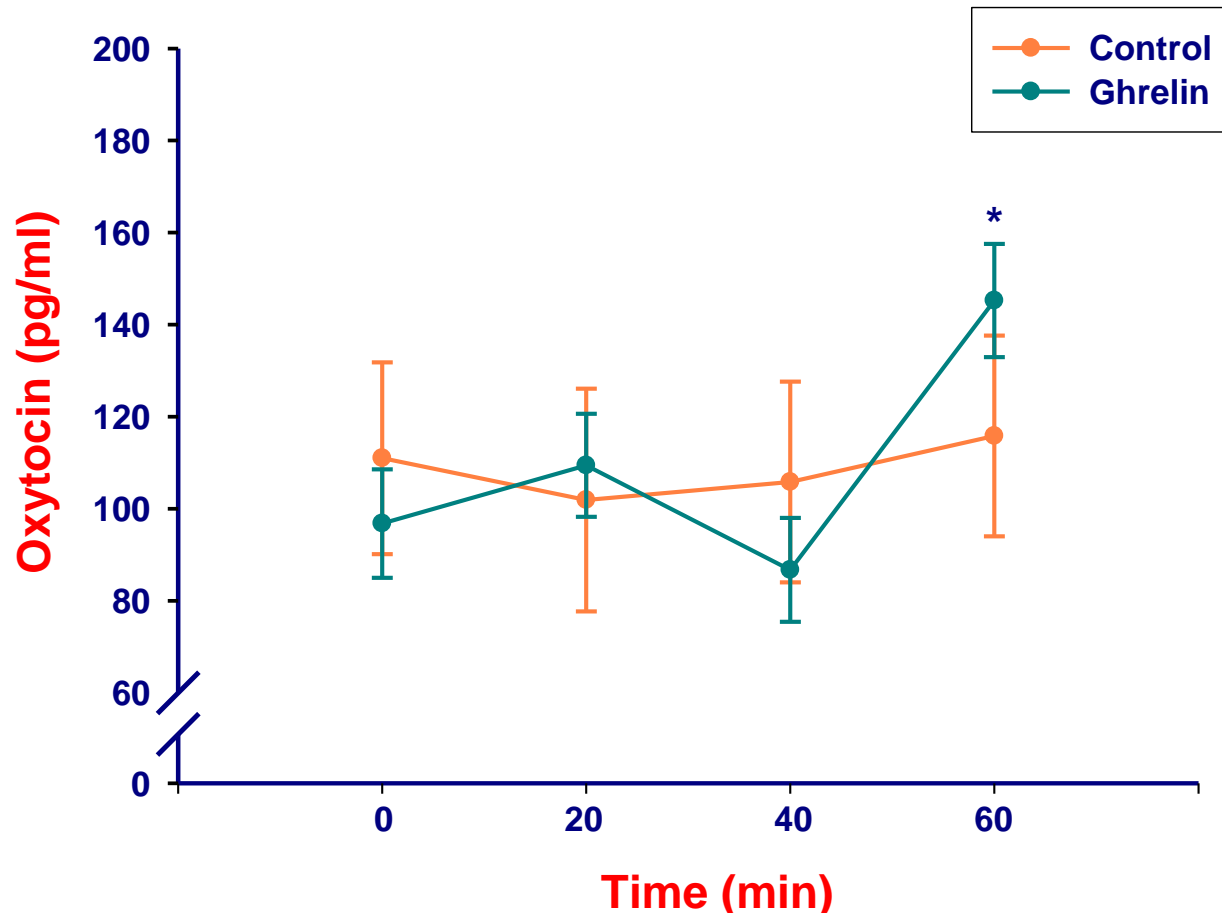


Fig 4. Oxytocin values of CCK and leptin groups (Mean $\pm$ SEM). \*p<0.05.



**Fig 5.** Oxytocin values of control and ghrelin groups (Mean±SEM). \*  $p < 0.05$

# Conclusion:

- ▶ These results indicate that CCK has stimulatory effect on plasma oxytocin level and NA content in the PVN.
- ▶ Leptin has modulatory effect on CCK induced oxytocin secretion. This modulation may occur through the inhibiting of NA release in PVN.

- ▶ **PVN is an important center for feeding behavior.**
- ▶ **It is known that administrations of noradrenaline and an alpha-2 adrenoreceptor agonist into the PVN induce food intake.**
- ▶ **Thus, modulatory effect of leptin on NA release in PVN may be related to feeding.**

▶ This study also revealed a stimulatory action of ghrelin on oxytocin secretion. Noradrenaline is not involved in the stimulation of oxytocin release by ghrelin.

▶ In another study, plasma ghrelin concentrations were found to be low during the initial periods and to increase towards the end of pregnancy in rats. Therefore, ghrelin may have a role in the activation of oxytocin neurons prior to parturition.

## **In conclusion;**

**Leptin may inhibit oxytocin secretion by lowering noradrenergic neurotransmission in the PVN. We also suggest that the modulatory effect of leptin on noradrenaline release in the PVN may be related to feeding behaviour.**

**We have also shown that ghrelin may stimulate oxytocin secretion without affecting noradrenaline concentration in the PVN.**



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