

Opposing effects of subtype-specific CRF receptor activation in the adBNST on maternal care and the stress axis in lactating rats

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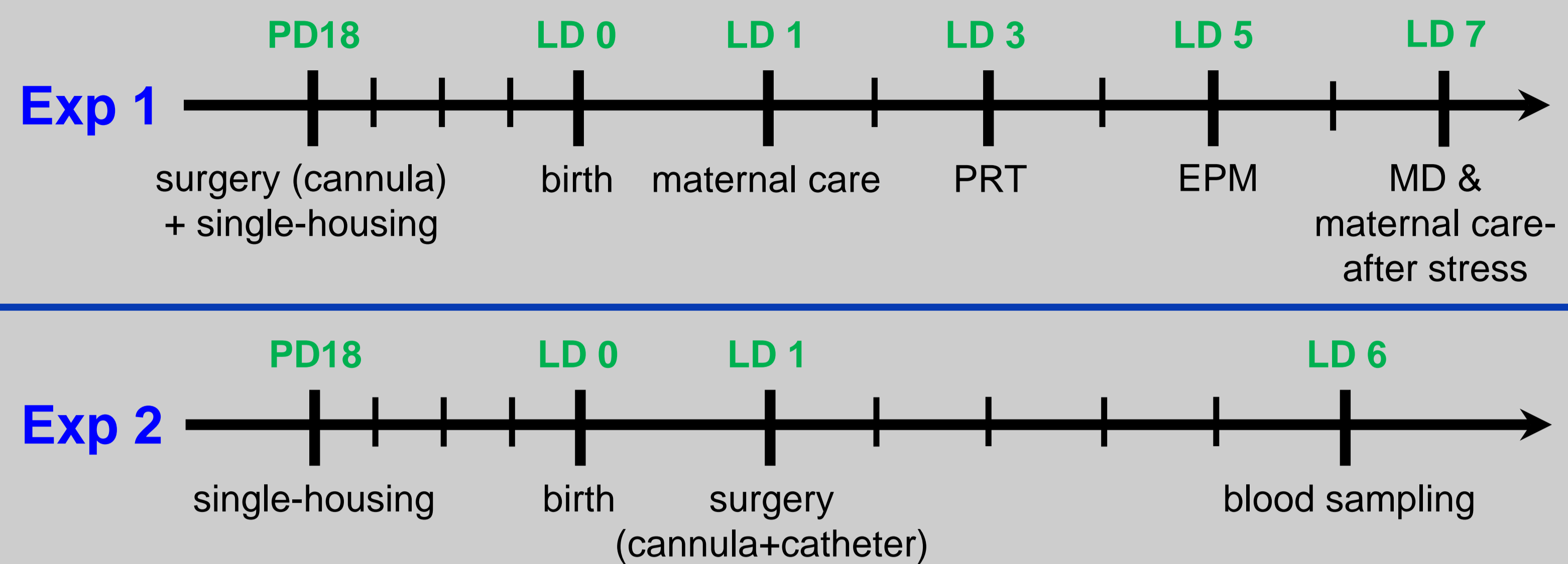
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Background

- 20 – 30 % of mothers develop postpartum mood disorders and even show child neglect.¹
- Maternal behavior is impaired by activation of central corticotropin-releasing factor receptors (CRF-R1/2) in lactating rats² and mice³.
→ predominantly mediated by CRF-R2 in the medial-posterior part of the bed nucleus of the stria terminalis (mpBNST; unpublished) in rats.
- The BNST functions as a central relay station and its subnuclei often exert opposing functions, especially in the stress response.⁴

Experimental design



Hypothesis

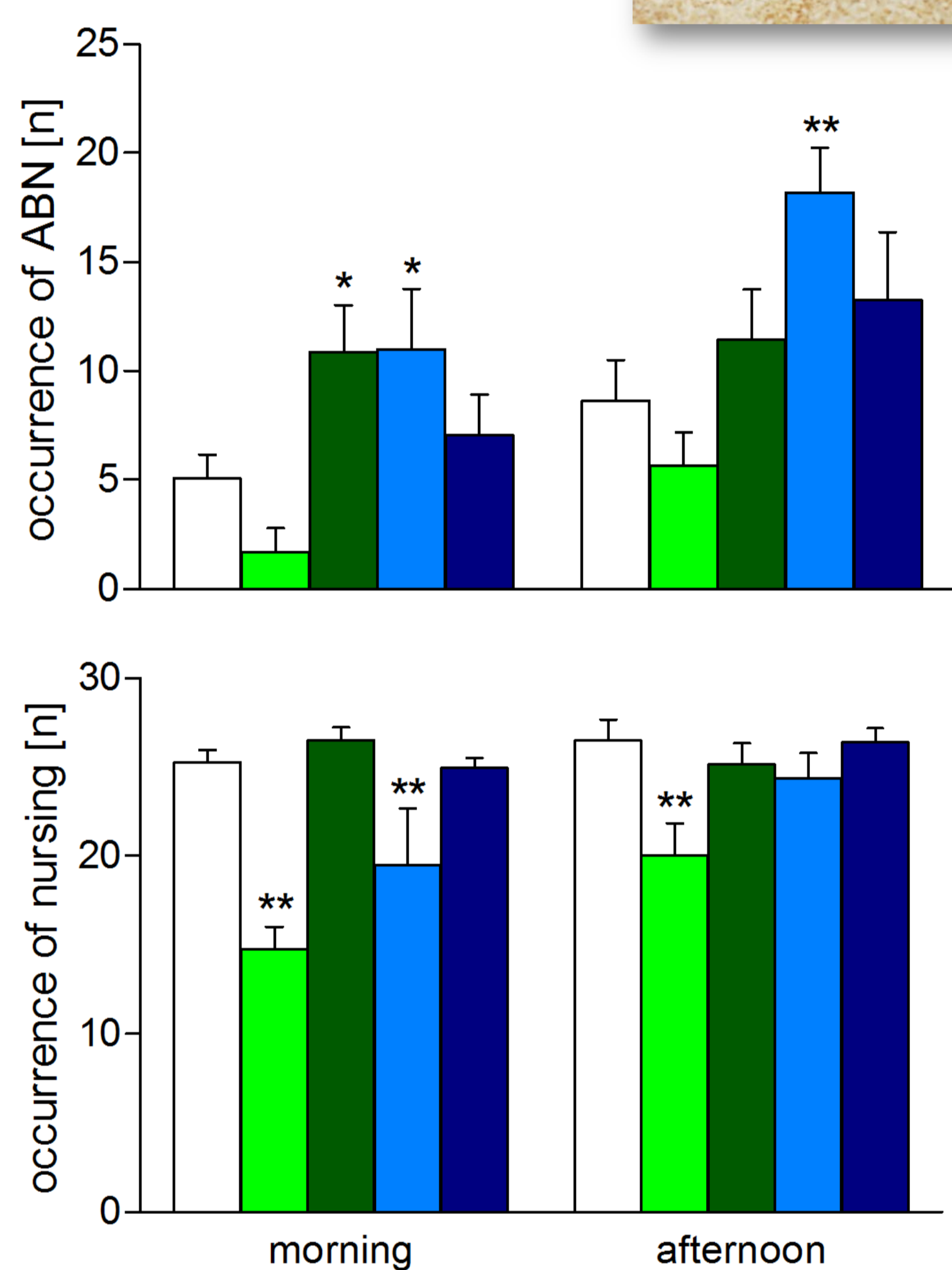
Subtype-specific activation of CRF-R in the anterior dorsal BNST (adBNST) modulates maternal behavior and hypothalamo-pituitary-adrenal (HPA) axis activity differently from the mpBNST in lactating rats.

Exp 1

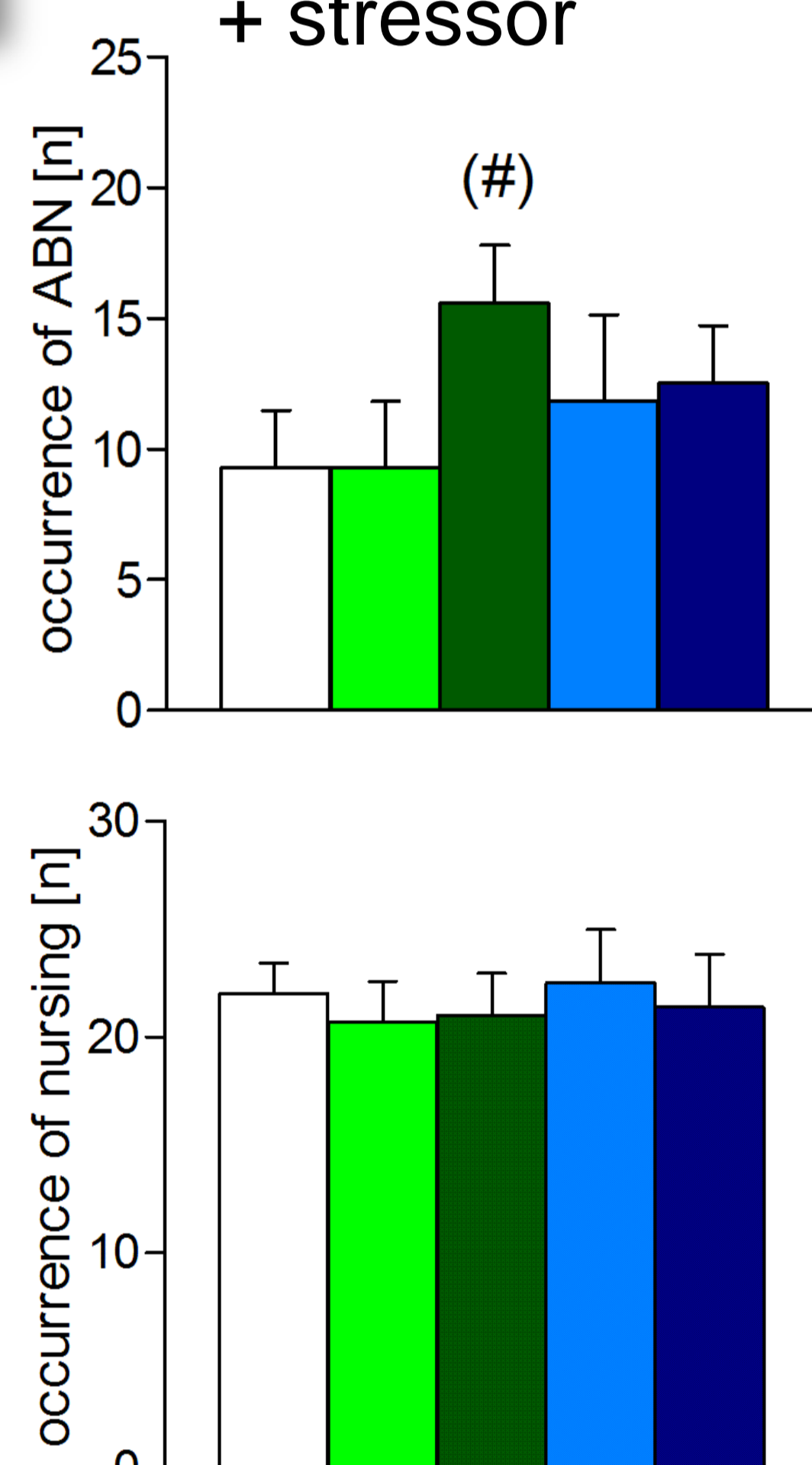
- Results -

Exp 2

Maternal care ...post-infusion



Maternal care ...post-infusion + stressor



→ ABN (quality of nursing) improved by CRF-R1 ant and CRF-R2 ago
→ total nursing (quantity of nursing) impaired by both agonists

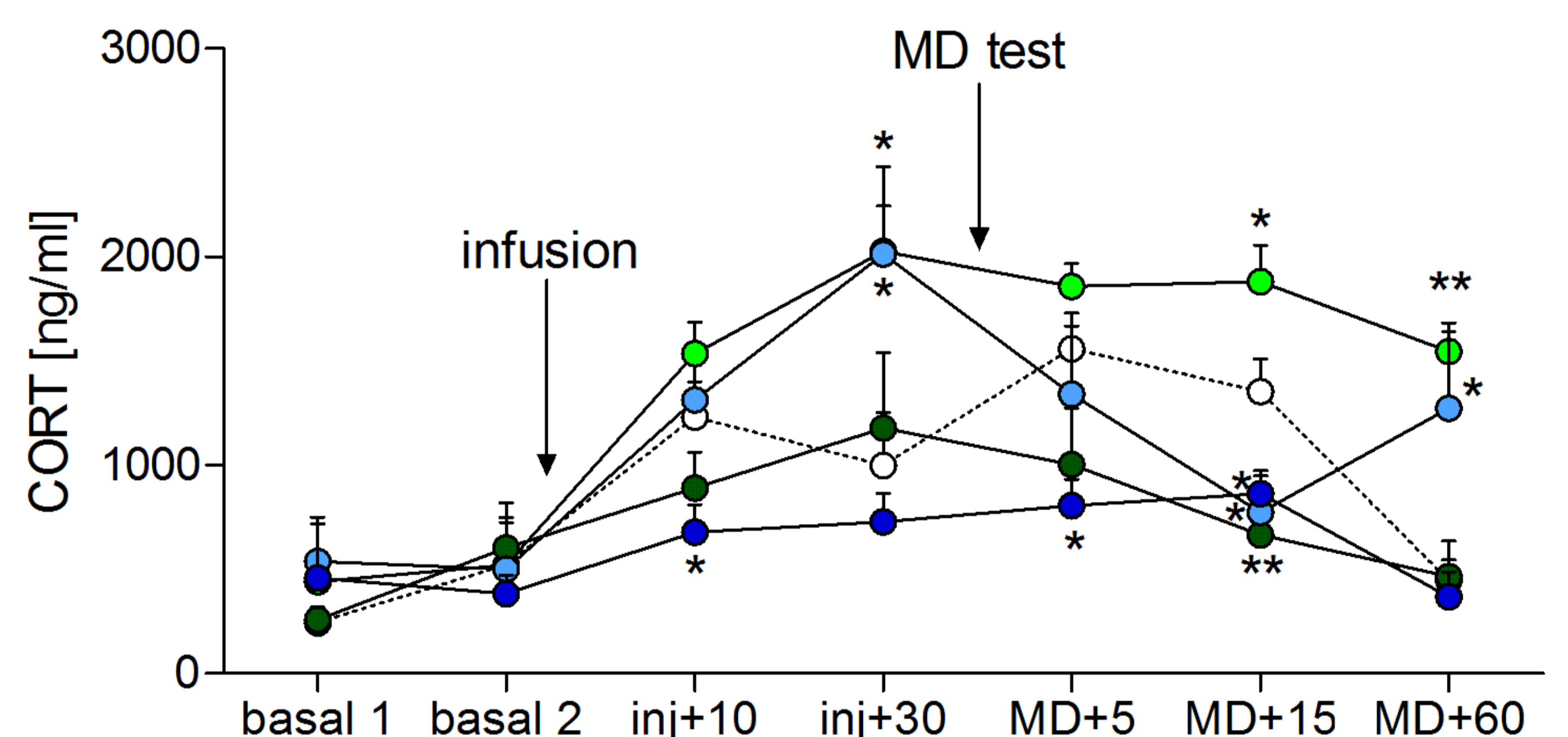
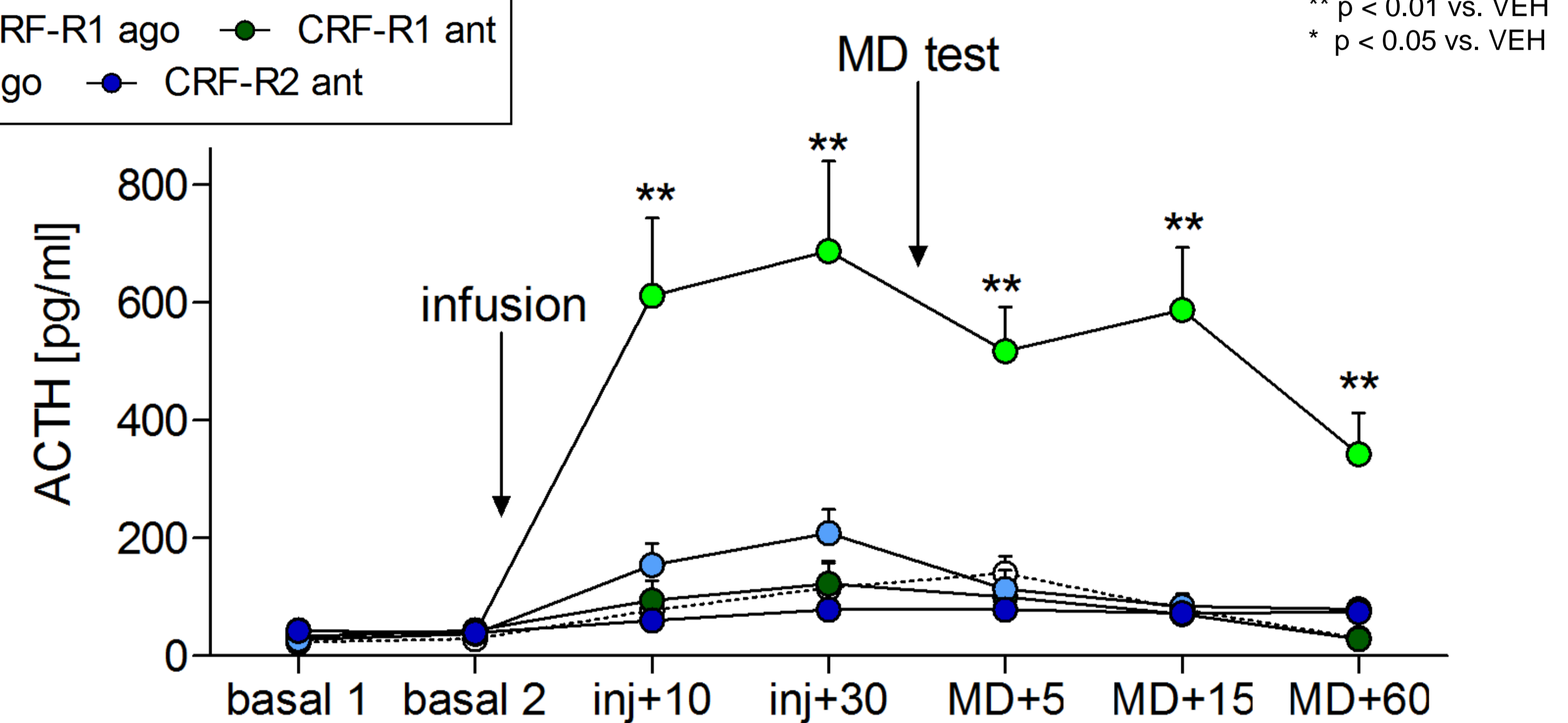
→ ABN improved/rescued by CRF-R1 ant only

** p < 0.01 vs. VEH
* p < 0.05 vs. VEH
(#) p 0.06 in sep. statistics

No effects of selective CRF-R manipulation in the adBNST on maternal motivation, maternal aggression, and anxiety.

Conclusion

- CRF-R1 and CRF-R2 mediate maternal care in the adBNST in opposing directions in contrast to their cooperation in the mpBNST (unpublished).
- Intra-adBNST activation of both CRF receptors activates the HPA axis under basal conditions while in stressful situations CRF-R1 and CRF-R2 act in opposing directions.
- Activation of the HPA axis by intra-adBNST manipulation potentially modulates maternal care via an indirect pathway.



Post-infusion

→ ACTH release increased by CRF-R1 ago only, CORT release increased by both agonists

Post-infusion + stressor (MD test)

→ ACTH and CORT level remain high in CRF-R1 ago-treated dams
→ switch in CORT release by CRF-R2 ago
→ both antagonists prevent the stressor-induced rise of CORT

Methods

Animals

Lactating Sprague-Dawley rats (230 – 250 g; CRL); n = 6 - 8 per group.

Local infusion of VEH, CRF, CP-154,526, Stresscopin, or Astressin-2B

• Implantation of bilateral local guide cannula (23G) targeting the adBNST (0.2 mm rostral, 3.0 mm lateral, 4.9 mm ventral, 12.5° angle) on PD 18 (Exp 1) or LD 1 (Exp 2). In Exp 2, a jugular vein catheter was additionally implanted.

• On LD 1, 3, 5, and 7 (Exp 1) or LD 6 (Exp 2) local infusion of 0.5 µl VEH (Ringer + 4% DMSO), CRF (CRF-R1 agonist; 1 µg), CP-154,526 (CRF-R1 antagonist; 12 µg), Stresscopin (CRF-R2 agonist; 3 µg), or Astressin-2B (CRF-R2 antagonist; 4 µg).

Maternal care observation

• Observation of arched back nursing (ABN) and different nursing positions every 2nd minute and averaged to 60 min in the home cage.

Pup retrieval test (PRT)

• Test for maternal motivation. Measurement of number of retrieved pups during a 15 min test in a novel environment.

Maternal defense (MD) test

• Observation of aggressive and non-aggressive behaviors displayed by the resident towards a virgin intruder for 10 min.

Elevated plus-maze (EPM)

• Test for anxiety-related behavior. Measurement of percentage of time spent on the open arms and number of closed arm entries for 5 min.

Blood sampling procedure

• Connection of jugular vein catheter to silicon tubing + syringe 1.5 h before first sample. Sample volume was 0.2 ml and substituted by NaCl.

• 2 samples were drawn under basal conditions, 2 samples 10 and 30 min after infusion, and 3 samples 5, 15 and 60 min after the MD test.

• Blood samples were centrifuged (15 min, 4 °C, 5000 rcf) and plasma was stored at -20° C until further processing. Adrenocorticotrophic hormone (ACTH) and corticosterone (CORT) concentrations were measured via ELISA.

References

- 1) Magiakou et al. (1996) J Clin Endocrinol Metab: 1912-7
- 2) Klampfl et al. (2013) Eur J Neurosci. 38: 2742-50.
- 3) Gammie et al. (2004) Behav Neurosci 118: 805-14
- 4) Crestani et al. (2013) Curr Neuropharmacol: 141-59

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Disclosure

No potential conflict of interest.