

## INTRODUCTION

Gastrin-releasing peptide (GRP) is the mammalian homologue of reptilian bombesin (BB). BBs appear to have anxiolytic and antisocial effects. In this regard, microinjection of GRP into the paraventricular thalamic nucleus decreased social<sup>1</sup>. Furthermore, GRP, with both central and peripheral administration, increases HPA activation as demonstrated by increased plasma levels of ACTH and corticosterone<sup>2</sup>. To date, the majority of the data on behavioral and physiological effects of GRP in rodents has been obtained using central or peripheral injection<sup>3</sup>. Most recently however, the intranasal route of drug administration has garnered considerable interest, particularly with respect to peptide administration in humans. Unlike central injection which is impractical for human subjects, or systemic injection, which is highly inefficient due to the inability of large peptides to cross the blood-brain barrier (BBB), intranasal delivery is non-invasive and can effectively bypass the BBB, allowing compounds to enter many sites in the brain<sup>4</sup>.

With this in mind, the aim of the present investigation is to examine the effects of intranasal GRP administration on social interaction and HPA functioning in rats and compare these effects with those elicited by the more traditional route of administration; systemic (intraperitoneal) injection.

## MATERIALS AND METHODS

**Subjects:** Male Sprague-Dawley rats (250-300 g.) housed individually for one week prior to behavioral testing and maintained under standard animal room conditions

**Drugs:** GRP was dissolved in 0.9% saline and administered intranasally at doses of 5µg and 20µg/20µl. The same doses were used for the intraperitoneal (i.p.) study however the injection volume was increased to 100 µl. Controls received an equivalent volume of saline. Pilot work in our lab confirmed that similar dosages for GRP would be appropriate..

**Intranasal Delivery:** 3-day habituation routine. Intranasal grips were done by trained experimenter and drug was applied bilaterally to the highly innervated rhinarium with direct application to the nostrils avoided (Figure 1a).

**Social Interaction:** 3 day paradigm: 2 days of habituation and 1 day testing (10 minutes in the box). Five social behaviours were monitored: sniffing, following, over and under, allogrooming, play fighting. Locomotor activity was also assessed (Figure 1b).

### Corticosterone levels in plasma:

Indirect measure of HPA acid activity by performing tail nix and blood collection.

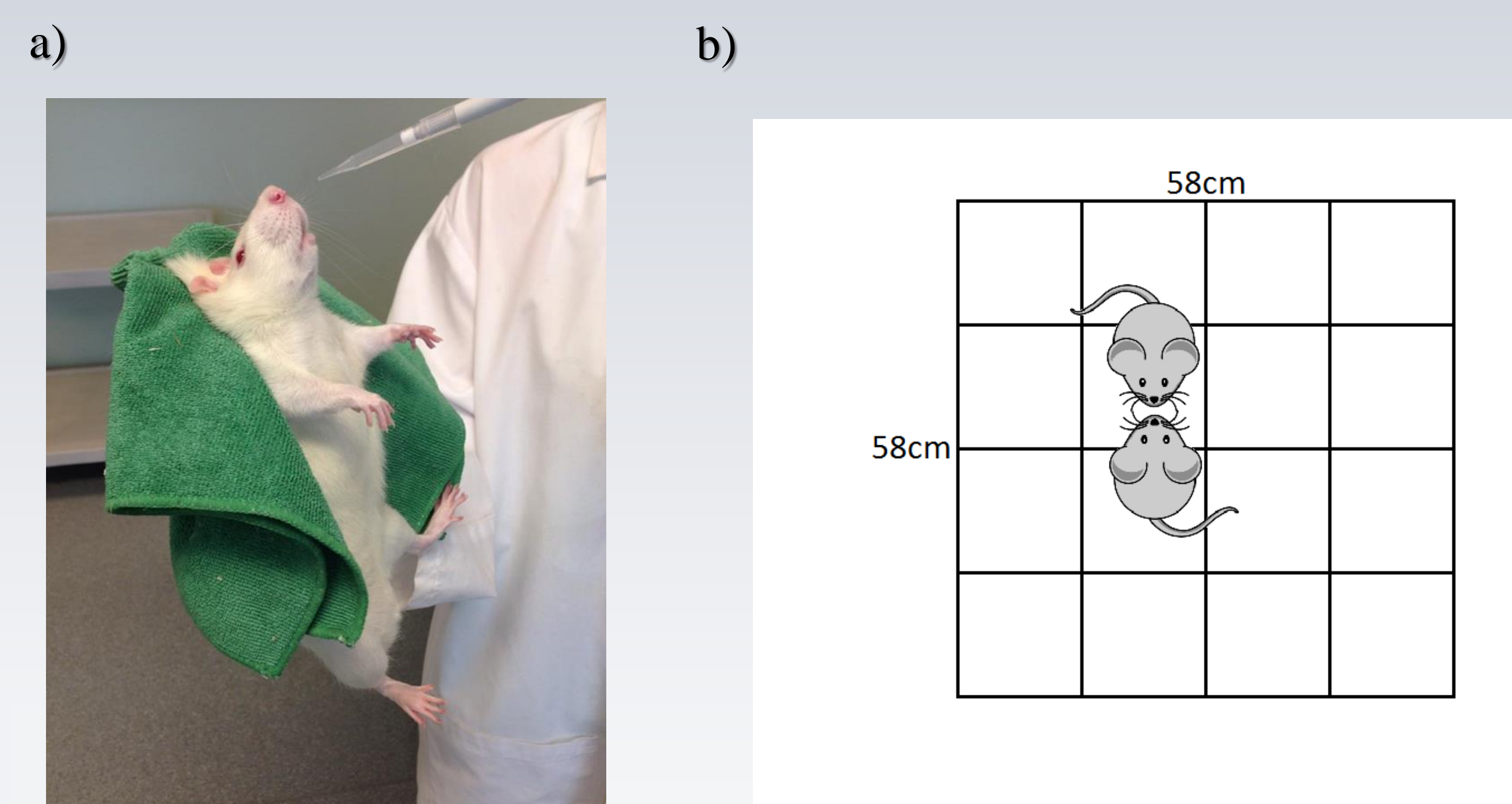


Figure 1. a) Intranasal Delivery

b) Social Interaction set up

## RESULTS

### Social Interaction

As depicted in Figure 2a, intranasal administration of GRP significantly decreased levels of active social interaction  $F(2, 21) = 3.93$   $p < 0.035$ . Follow up tests confirmed that only the 20 µg dose of GRP was effective. Similar to effects observed with intranasal peptide administration, as shown in Figure 2a, i.p. injection of GRP decreased ( $F(1,21) = XX$ ) levels of active social interaction (Figure 2b). Follow up comparisons further revealed that i.p. injection of 5 and 20 µg of GRP significant decreased the amount of time spent engaged in active social interaction.

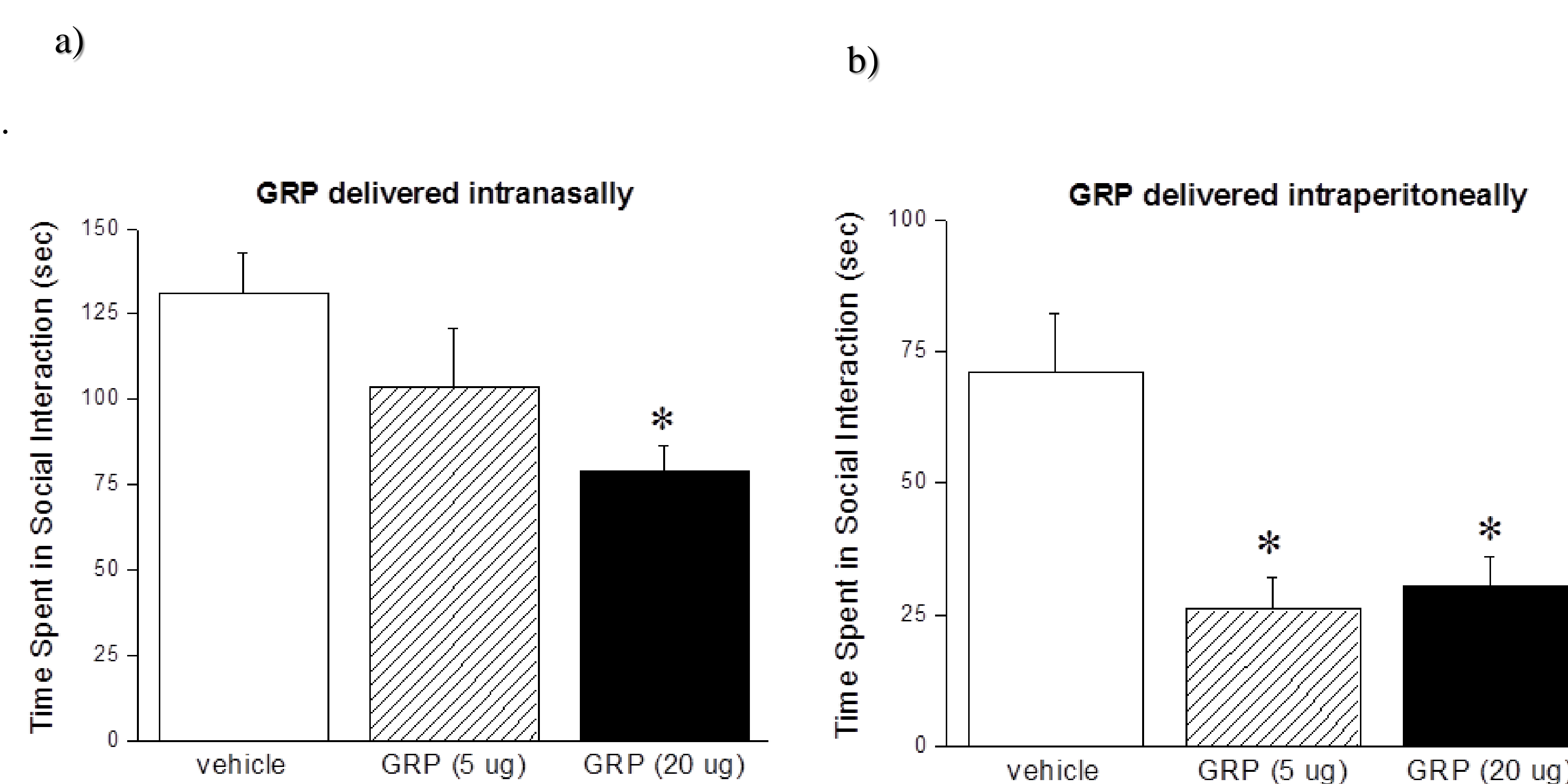


Figure 2. a) GRP delivery intranasally

b) GRP delivery intraperitoneally

### Corticosterone Analysis

Figure 3 shows blood levels of corticosterone at baseline and 20, 40, 60 and 120 min following intranasal administration of GRP (20 µg). Intranasal administration of GRP demonstrated an increase in corticosterone levels but there was no significant effect with intraperitoneal administration.

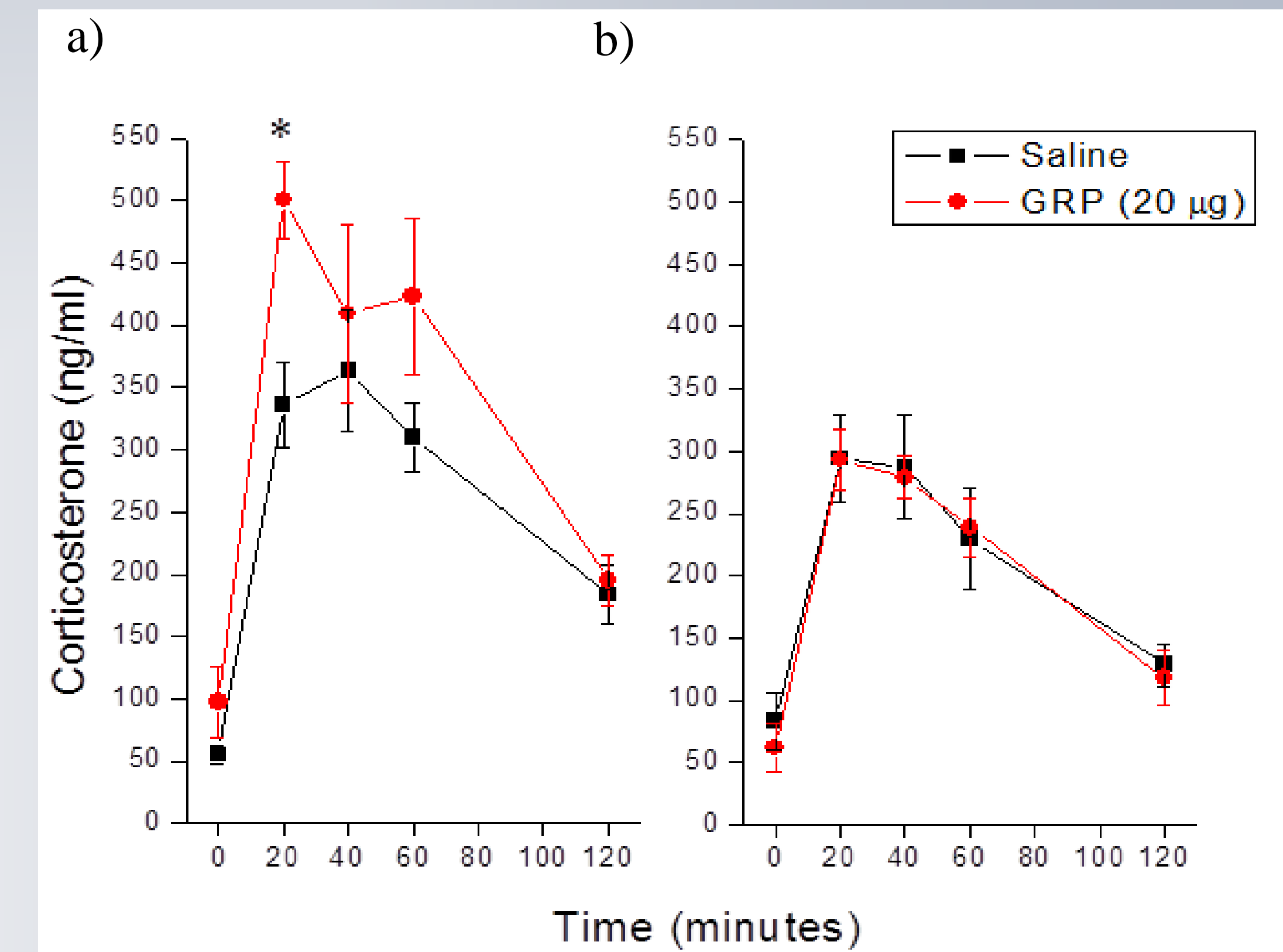


Figure 3. a) GRP delivery intranasally

b) GRP delivery intraperitoneally

## CONCLUSION

- Intranasal route of administration is an effective means of peptide drug delivery
- Intranasal GRP decreases male-male social interaction in rats
- Intranasal delivery is comparable to intraperitoneal delivery of peptide drugs
- GRP activates the HPA axis via a central mechanism.
- Exploring the effects of intranasal administration of GRP is useful considering bombesin-family peptide antagonists have anxiolytic properties<sup>1</sup> and could be used as a treatment for anxiety and stress disorders.
- Therefore, the potential to administer bombesin family receptors intranasally as anxiolytic treatment exists.

## ACKNOWLEDGMENTS

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