# TESOFENSINE, A NOVEL TRIPLE MONOAMINE REUPTAKE INHIBITOR, INDUCES APPETITE SUPPRESSION BY COMBINED STIMULATION OF $\alpha_1$ ADRENOCEPTOR AND $D_1$ DOPAMINERGIC RECEPTOR PATHWAYS IN THE DIET-INDUCED OBESE RAT

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NEUROSEARCH

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## INTRODUCTION

Tesofensine is a novel monoamine reuptake inhibitor (MRI) which inhibits both norepinephrine, 5-HT and dopamine reuptake function. Tesofensine is currently in clinical development for the treatment of obesity and in the study by Astrup et al. (*Lancet* 372:1906-1913, 2008) Tesofensine has been shown to have appetite-suppressant effects in obese patients, however, the pharmacological basis for this effect is not clarified. Using a rat model of diet-induced obesity (DIO), we characterized the pharmacological mechanisms underlying the appetite suppressive effect of tesofensine.

## METHODS

A diet-induced obesity (DIO) model was obtained by feeding male Sprague Dowley rats a high fat diet (60% fat kcal) for 2 months. This model was used to assess the interaction of a variety of monoamine receptor antagonists with tesofensine-induced hypophagia in an automatized real-time food intake monitoring system (HM-2 MBRose, Faaborg, Denmark, see figure insert). The DIO rats were tagged with an RFID chip (s.c.) and allowed to habituate to the HM-2 system for at least 5 days before drug testing. Tesofensine was dissolved in saline and all monoamine receptor antagonists were dissolved in hydroxypropyl-β-cyclodextrin. All drugs and vehicle were administered subcutanously just before dark onset. Food intake was monitored during the 12h nocturnal period.

## RESULTS

Tesofensine (0.5-3.0 mg/kg, s.c.) induced a dose-dependent and marked decline in food intake. The hypophagic response of tesofensine (1.5 mg/kg, s.c.) was almost completely reversed by co-administration of prazosin (1.0 mg/kg, $\alpha_1$ adrenoceptor antagonist) and partially antagonized by co-administration of SCH23390 (0.03 mg/kg, dopamine $D_1$ receptor antagonist). In contrast, tesofensine-induced hypophagia was not affected by RX821002 (0.3 mg/kg, $\alpha_2$ adrenoceptor antagonist), haloperidol (0.03 mg/kg, $D_2$ receptor antagonist), NGB2904 (0.1 mg/kg, $D_3$ receptor antagonist), ritanserin (0.03 mg/kg, 5-$HT_{2A/C}$ antagonist). All monoamine receptor antagonists showed no effect on food intake per se.

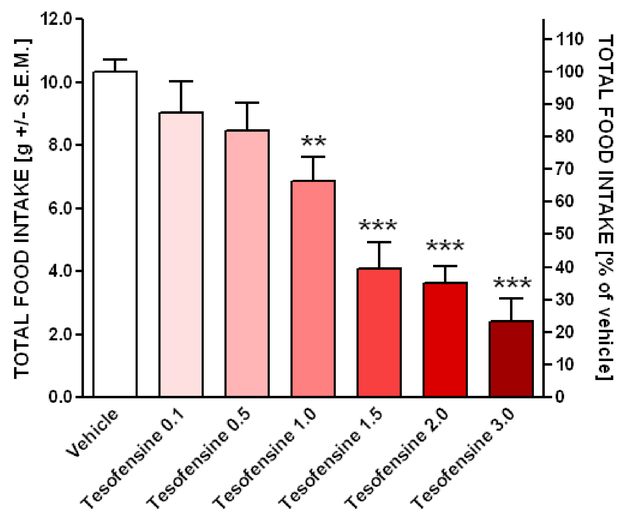
## CONCLUSION

The mechanisms underlying the appetite suppressant effect of tesofensine is based on the drug's ability to simultaneously stimulate $\alpha_1$ adrenoceptor and dopamine $D_1$ receptor function subsequent to blocked reuptake of norepinephrine and dopamine.

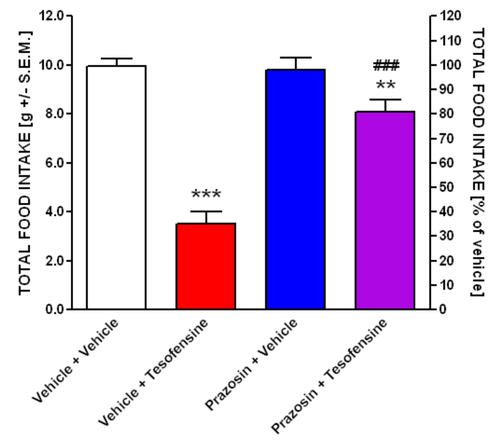
### THE HM-2 SYSTEM - REAL TIME MONITORATION

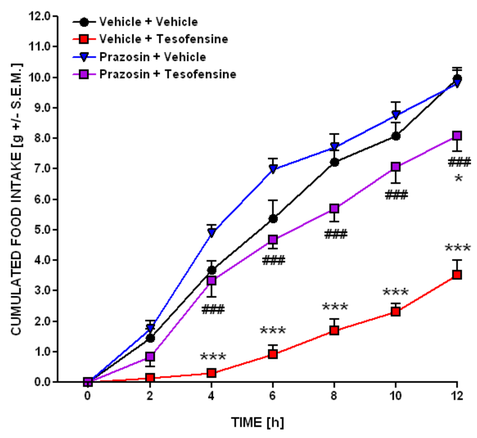
The HM-2 system monitors food and water intake as well as total locomotor activity in real-time. Food intake is registered by RFID tagging of two individual DIO rats in the same cage while locomotor activity is registered by an infrared sensor.

### A DOSE-RESPONSE OF TESOFENSINE
#### - TESOFENSINE INHIBITS ACUTE FOOD INTAKE

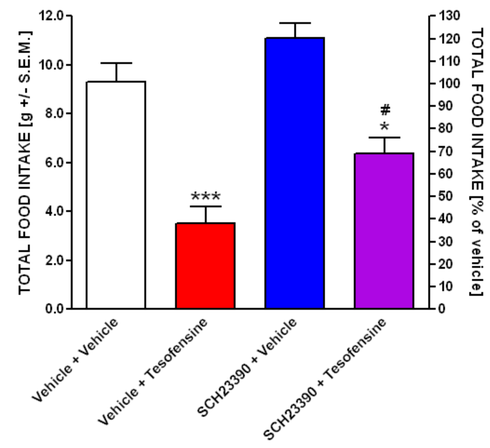


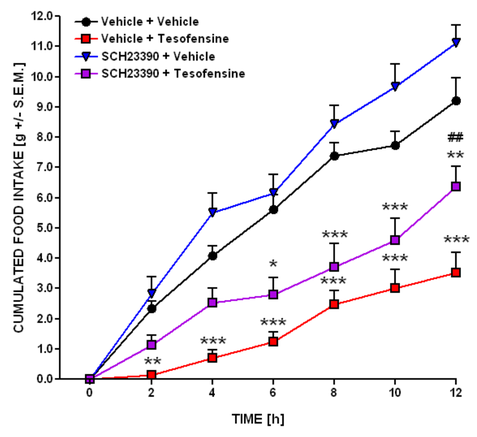

### B BLOCKADE OF $\alpha_1$-ADRENOCEPTORS
#### - PRAZOSIN BLOCKS THE HYPOPHAGIC RESPONSE TO TESOFENSINE



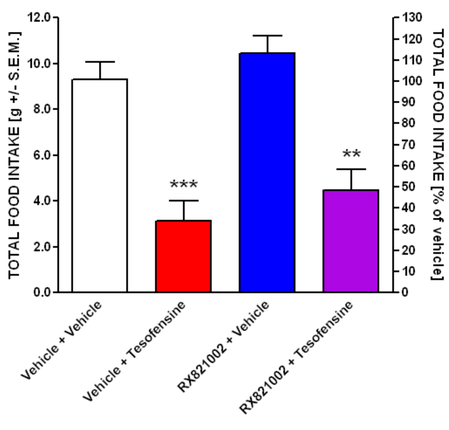



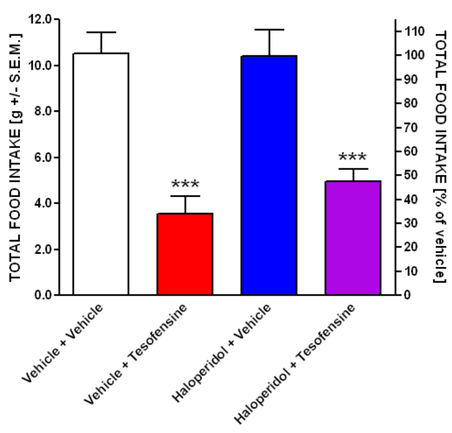

### C BLOCKADE OF $D_1$-RECEPTORS
#### - SCH23390 PARTIALLY BLOCKS THE HYPOPHAGIC RESPONSE TO TESOFENSINE

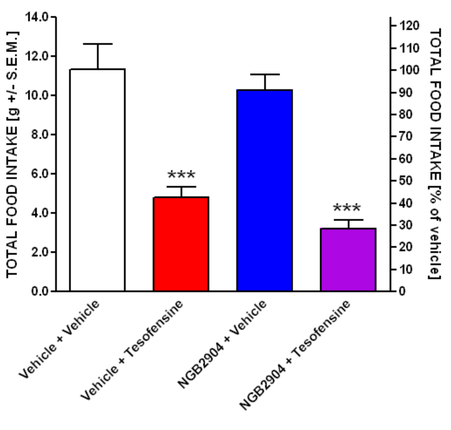



### D BLOCKADE OF $\alpha_2$-ADRENOCEPTORS, $D_2$-, $D_3$ AND 5-$HT_{2C/A}$-RECEPTORS
#### - RX821002, HALOPERIDOL, NGB2904 AND RITANSERIN DOES NOT BLOCK THE HYPOPHAGIC RESPONSE TO TESOFENSINE



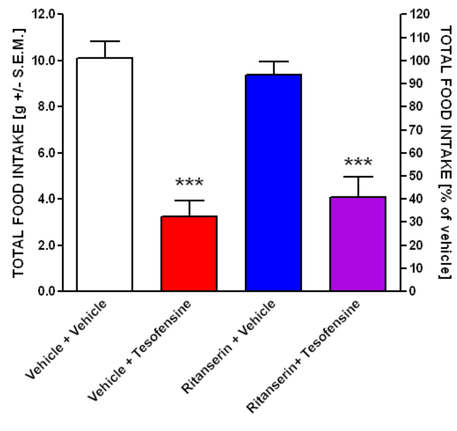




**Figure A, B, C and D.**
Showing total food intake and accumulated food intake (only B and C) during the 12 hour nocturnal period after administration of the drugs indicated. Left Y-axis indicates food intake in grams while the right Y-axis shows percentage food intake relative to vehicle (100%). Data analysis using a one-way (total food intake) or two-way (time-response effect) ANOVA.*p<0.05, **p<0.01, ***p<0.001 when compared to vehicle and #p<0.05, ##p<0.01, ###p<0.001 when compared to tesofensine.