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## Endogenous Oxytocin Response to Food Intake in Avoidant/Restrictive Food Intake Disorder Compared to Healthy Controls

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**Context:** In healthy individuals, serum levels of oxytocin, an anxiolytic hypothalamic-pituitary hormone involved in appetite regulation and response to stress, decrease post-prandially. Oxytocin response to a meal in Avoidant/Restrictive Food Intake Disorder (ARFID), a psychiatric disorder characterized by restrictive eating driven by lack of interest in food, sensory sensitivity, and/or fear of aversive consequences and associated with comorbid anxiety, is unknown. We compared the pattern of postprandial oxytocin levels in individuals with ARFID to healthy controls (HC). We hypothesized that overall oxytocin levels would be higher in ARFID vs HC as an adaptive response to stress.

**Methods:** 109 participants (55 with ARFID and 54 HC) were instructed to eat a ~400-kcal standardized mixed meal. Serum oxytocin was sampled fasting and 30, 60, and 120 minutes post-meal. Anxiety was assessed using the trait scale of the State-Trait Anxiety Inventory (STAI). All data are presented as mean±SEM. Multivariate regression analysis was used to control for confounding variables.

**Results:** Mean age did not differ across groups (ARFID: 16.9±0.5 and HC: 17.8±0.5 years, p=0.197). Mean body mass index percentile (BMIp) was lower in ARFID compared to HC ( $37.3\pm4.9$  vs  $53.7\pm2.9$ , respectively, p=0.004). Sex distribution differed between groups [ARFID: 27 (50%) males, 27 (50%) females vs HC: 15 (27%) males and 40 (73%) females, p=0.019)]. Anxiety symptoms were higher in ARFID compared to HC ( $38.5\pm1.8$  vs  $30.3\pm1.0$ , respectively, p=0.0007). By study design, quantity of food consumed did not differ across groups (p=0.238), however, ARFID participants ate a higher % of fat than HC ( $22.8\pm0.5$  vs.  $21.6\pm0.4$ , p=0.027). Mean oxytocin levels were higher in ARFID compared to HC at all time points (fasting: 1487±94 vs 1268±60 pg/mL, p=0.049; 30 min: 1477±86 vs 1202±48 pg/mL, p=0.006; 60 min: 1473±89 vs 1214±52 pg/mL, p=0.015; 120 min: 1470  $\pm 102$  vs  $1253\pm 50$  pg/mL, respectively, p=0.056), and AUC (p=0.023). While mean oxytocin decreased postprandially as expected in HC (30 min p=0.028 and 60 min p=0.072), there was no postprandial change in oxytocin levels in ARFID from fasting to any postprandial timepoint ( $p \ge 0.746$ ). Multivariate regression analysis revealed that both ARFID group ( $\beta$ =41,213,  $\eta^2 p$  = 0.084, p=0.004) and BMIp ( $\beta$ =779,  $\eta^2 p = 0.129$ , p<0.001) accounted for higher oxytocin levels irrespective of sex, fat intake and anxiety levels ( $R^2=0.192$ ).

**Conclusions:** This is the first study to determine the pattern of endogenous oxytocin secretion in response to a meal in a large group of individuals with ARFID. Mean oxytocin levels fasting and in response to a meal are higher in ARFID compared to HC, irrespective of sex, quantity of fat consumed, and anxiety symptoms. Unlike in healthy individuals, oxytocin levels in ARFID do not decrease in response to eating. These data suggest that dysregulated oxytocin secretion may play a role in the pathophysiology of ARFID.

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