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Elevated levels of non-esterified fatty acids (NEFA) have been observed in individuals with several clinical scenarios of insulin resistance, such as in diabetes mellitus and lipodystrophy. Insulin is a well-known stimulator of *de novo* lipogenesis. Despite the reduction of adipose tissue mass, paradoxically elevated circulating NEFA concentrations have been observed in patients with different lipodystrophy syndromes. Aiming to understand the behavior of NEFA in lipodystrophy versus common Type 2 diabetes mellitus during feeding, we compared NEFA kinetics during a mixed meal test in patients with partial lipodystrophy (PL) and Type 2 diabetes mellitus (DM). We reviewed data from 17 PL patients (13F/4M, ages 12–64) matched by gender and BMI to 20 DM patients (13F/7M, ages 24–72). All patients were evaluated during fasting state and then underwent a mixed meal test (MMT). Blood samples were collected before (fasting) and at 30, 60, 90, 120, and 180 minutes post-meal to measure glucose, insulin, non-esterified free fatty acids (NEFA), and triglyceride levels. Adipose tissue insulin resistance (ADIPO-IR) and homeostatic model of insulin resistance (HOMA-IR) were calculated from the fasting measurements, and the area under the curve (AUC) and maximum percentage of change from baseline were calculated from the MMT data. Fasting insulin and triglyceride (Tg) levels were lower in the DM group compared to the PL group (Insulin: 24.4±13.7 vs. 68.0±67.2 pmol/L, p=0.003 and Tg: 168.0±107.7 vs. 1378.3±1927.3 mg/dL, p<0.001). HOMA-IR was significantly higher in the PL group compared to the DM group (6.0±2.1 vs. 3.3±1.5, p=0.005), as well as ADIPO-IR (297.0±241.1 vs. 115.3±80.1, p=0.03). NEFA, glucose and triglyceride AUC were significantly higher in the PL group compared to the DM group. Patients with PL had higher glucose and triglyceride levels throughout the MMT at all-time points. Interestingly, NEFA levels were similar in both groups at baseline, but the PL group suppressed NEFA less than DM group (54.9±13.3% vs. 69.2±11.1%, p=0.002) despite higher insulin levels. Additionally, we divided the PL group according to the presence of a pathogenic variant in the *lamin A* gene (n=8) versus those without mutations in this gene (n=9), but there were no notable differences among these subgroups with respect to NEFA levels at baseline or during the meal. These findings support the need to better understand and address the origins of abnormal NEFA kinetics and adipose tissue insulin resistance in PL patients.

Adipose Tissue, Appetite, and Obesity

INTEGRATED PHYSIOLOGY OF OBESITY AND METABOLIC DISEASE

Absence of Sex Differences Identified in Food Motivation Pathways in Youth with Avoidant/ Restrictive Food Intake Disorder (ARFID)

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Background: Avoidant/Restrictive Food Intake Disorder (ARFID) is a recent diagnosis incorporated into the *DSM-5* to provide diagnostic specificity to individuals who may have avoidant/restrictive eating behavior unrelated to body image/weight concerns and display three core profiles: insufficient intake/low interest in feeding, fear of aversive consequences related to food intake (e.g., choking) and avoidance based on sensory characteristics of food. Various studies have shown a higher preponderance of male patients in ARFID compared to other eating disorder groups. To elucidate potential sex differences in the neurobiology of ARFID, we examined food motivation pathways by assessing levels of key appetite regulating hormones, anorexigenic peptide YY (PYY) and orexigenic ghrelin, and fMRI activation of relevant brain circuitry in females compared to males with ARFID. Based on prior fMRI studies in healthy controls, we hypothesized that in a fasted state, females (vs. males) would demonstrate greater blood-oxygen-level-dependent (BOLD) activation in response to high-calorie food (vs. non-food) images in the orbitofrontal cortex (OFC) and the right lateral prefrontal cortex (LPFC), while males (vs. females) would demonstrate greater activation in the right hippocampus.
Methods: Seventy-five adolescents and young adults with ARFID and sub-threshold ARFID (43 female) were studied after a 10-hour overnight fast. PYY and ghrelin levels were assessed in a subset of 62 individuals (31 female). All participants completed fMRI imaging in a 3T scanner while viewing images of foods, non-food items, and fixation stimuli. Functional MRI data were analyzed using SPM12. A priori regions of interest included the right lateral prefrontal cortex (LPFC), right hippocampus and orbitofrontal cortex (OFC). Secondary exploratory whole-brain analysis was also performed. Statistical significance is reported at the p<0.05 level.
Results: Females and males did not differ in age ((mean±SD): 16.1±3.7 years) or BMI (19.9±5.4 kg/m^2). There were no statistically significant differences between females and males in PYY (p=0.10) or ghrelin (p=0.47) levels. Furthermore, analysis of fMRI data yielded no significant differences between females and males with ARFID in a priori regions of interest (OFC: p(FWE-corr)>0.50; R LPFC: no suprathreshold clusters, or R hippocampus: p(FWE-corr)=0.25 and 0.33) or in the secondary whole-brain analysis (cluster p(FWE-corr)=0.304).
Conclusion: This is the first study to investigate sex differences in the neurobiology of ARFID, an important line of research to advance treatment approaches. We found no sex-specific neurobiological differences in adolescents and young adults with ARFID. Future studies with larger sample sizes are needed to further investigate potential sex differences across the different ARFID profiles.