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Background: Obesity is a state of relative growth hormone (GH) and insulin-like growth factor-1 (IGF-1) deficiency, and the GH/IGF-1 axis has been implicated in the pathophysiology of nonalcoholic fatty liver disease (NAFLD) and the progression to steatohepatitis (NASH) in preclinical models and human studies. GH has both lipolytic and anti-inflammatory properties while IGF-1 has been implicated in reducing hepatic fibrosis and promoting hepatic regeneration. The GH/IGF-1 axis may be a therapeutic target in NAFLD/NASH, however, IGF-1, IGF-1 receptor (IGF-1R) and GH receptor (GHR) expression in adult human hepatic tissue has not been studied across the spectrum of disease severity.
Methods: We quantified IGF-1, IGF-1R, and GHR gene expression in hepatic tissue from 318 adults with obesity using the Nanostring nCounter assay. Subjects were classified into four categories of disease severity based on histopathology: normal liver histology (NLH) (n=76, 24%), steatosis only (Steatosis) (n=88, 28%), NASH without fibrosis (NASH F0) (n=72, 23%), and NASH with fibrosis (NASH F1-F4) (n=82, 26%). Gene expression analysis is presented as normalized gene counts by group with p-value of the generalized linear model controlled for age, sex and BMI.
Results: Mean (±SD) age (whole cohort 44.0±12 years) and BMI (whole cohort 46.8±7.2 kg/m^2) did not differ across groups (p=0.2 for both). ALT was higher with increasing disease severity (NLH 30.1±26.7, Steatosis 31.9±15.7, NASH F0 35.7±16.5, NASH F1-4 48.4±34.9, p<0.001). IGF-1 gene expression was lower in all NAFLD/NASH groups compared to the NLH reference group (NLH 485.4±292.7; Steatosis 396.3±238.0, p=0.04; NASH F0 349.8±220.1, p=0.01 and NASH F1-4 341.2±268.6, p=0.03, all p-values vs NLH). There was no difference in IGF-1R or GHR gene expression across disease severity groups (IGF-1R NLH 43.3±10.2, Steatosis 41.4±11.6, NASH F0 38.8±8.8 and NASH F1-4 39.1±8.1, p>0.05 between any disease state; GHR NLH 6382±2366, Steatosis 6544±2699, NASH F0 7220±2542 and NASH F1-4 5997±2352, p>0.05 between any disease state).
Conclusion: We demonstrated that IGF-1 gene expression was lower in liver tissue from patients with NAFLD and NASH than healthy controls. This is consistent with our prior finding that histologic NASH and fibrosis are associated with lower serum IGF-1 levels. Moreover, we demonstrated that hepatic IGF-1R and GHR gene expression is not lower in liver tissue from patients with NAFLD and does not decline across disease severity. This reinforces our prior finding that GHR staining intensity and zonality by immunohistochemistry does not change with increasing disease severity in NAFLD/NASH. These data demonstrate that the GH axis is relatively suppressed but that expression of GHR and IGF-1R receptors is stable with worsening disease severity in NAFLD/NASH, suggesting that GH augmentation may be a viable therapeutic target in NAFLD.

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Expression of Kisspeptin, Neurokinin B, and Dynorphin During Pubertal Development in Female Sheep

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Puberty onset depends upon an increase in pulsatile GnRH/LH secretion, which in sheep is the result of reduced sensitivity to estrogen negative feedback. Neurons within the arcuate nucleus of the hypothalamus (ARC) expressing kisspeptin, neurokinin B (NKB), and dynorphin (i.e. KNDy neurons) express estrogen receptors and are believed to play a key role in mediating the effects of estrogen on GnRH/LH secretion. Therefore, the purpose of this study was to assess changes in kisspeptin, NKB, and dynorphin within the ARC across pubertal development in female sheep. Blood samples were collected at 12-minute intervals for 4 hours and assessed for LH secretion in five age groups of ewes: 5 months (n=6), 6 months (n=6), 7 months (n=5), 8 months (n=5), and 10 months (n=6) of age. Following each bleed, ewes were sacrificed, hypothalamic tissue containing the ARC was collected, and then processed for use in dual immunofluorescence and RNAscope. Mean LH and LH pulse frequencies followed the expected patterns: concentrations and frequencies were low during the prepubertal ages (5-7 months of age), intermediate during the peripubertal age (8 months of age), and elevated in the postpubertal age group (10 months of age). Using immunofluorescence, kisspeptin and NKB immuno-positive cell numbers did not change significantly (P > 0.50) over time with cell numbers averaging 235.3±16.8 and 231.3±16.8, respectively. Colocalization of kisspeptin and NKB was greater than 90% for all age groups. Using RNAscope, the total number of cells expressing mRNA for kisspeptin and dynorphin did not change significantly (P > 0.05) over time with cell numbers averaging 46.7±12.0 and 28.3±10.0 cells/hemisection, respectively. Taken together, our data suggest that the increase in LH secretion that drives puberty onset is not limited by changes in kisspeptin, NKB, or dynorphin expression, but may instead depend on other factors such as changes in receptor expression or changes in KNDy neuron activity via a reduction in inhibitory and/or an increase in stimulatory afferent inputs.

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