results suggest a mechanism where near-UV sensitive hypothalamic OPN5 neurons regulate BAT thermogenesis directly, proposing that the mammalian autonomic thermoregulatory apparatus is light responsive.

Adrenal

ADRENAL - TUMORS

Distinct Vitamin D Receptor DNA Methylation Profiles Are Associated With the Outcome of Pediatric Patients With Adrenocortical Tumors

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SAT-LB36

Pediatric adrenocortical tumors (pACT) are rare, display complex genomic background and lack robust prognostic markers. Very recently, distinct genomic methylation profiles of pACT were associated with prognosis. The vitamin D receptor (VDR) was shown to be underexpressed in ACT, especially in carcinomas (ACC). In adult ACC, VDR inactivation by methylation was demonstrated. On the other hand, VDR activation was shown to inhibit ACC proliferation *in vitro* and *in vivo*.

Aim: To evaluate *VDR* DNA methylation profile and its clinical and prognostic significance in pediatric ACT.

Methods: Genomic DNA methylation from 57 pACTs [40 girls; median age: 2.1 (0.2-16.4) years] was assessed using Infininium Methylation EPIC BeadChip Array. Unsupervised hierarchical clustering analysis (Ward method, R Stats Package) was performed considering the M-values of the 49 probes targeting the whole extension of *VDR* gene contained in the array. Clinical, histopathological and molecular features, as well as pACT VDR mRNA levels (qPCR) and nuclear immunoreactivity (IHC) were used for association analysis.

Results: Hierarchical clustering identified three clusters of pACT. Methylated *VDR*-targeted probes (M-values different from 0; n=37) composed the *VDR* methylation profile, which differed significantly between the clusters [M-values: C1=1.77 (1.1-1.9) (low), C2=2.15 (1.7-2.7) (intermediate), and C3=2.65 (2.2-3.1) (high); $p<0.0001$]. The C1 cluster comprised a set of patients with favorable outcome (n=18), who were younger ($p=0.035$), did not present metastasis at diagnosis (IPACTR stage IV) or after surgery, nor were diagnosed with carcinomas (Wieneke criteria >=4), were not carriers of somatic Beta-catenin activating mutations, or died. Although cluster C2 patients (n=21) presented intermediary disease features, only 2 patients died and the overall outcome was positive. Instead, the C3 cluster concentrated patients (n=18) with non-localized/metastatic disease (IPACTR stages I/II *vs*. III/IV; $p=0.004$), post-surgical metastasis/recurrence ($p=0.009$), and patients who needed adjuvant chemotherapy ($p=0.005$). Moreover, C3 patients had lower overall and disease-free survival rates (log-rank: $p=0.001$ and $p=0.014$, respectively). *VDR* methylation was not associated with sex, clinical presentation, P53 mutations, nor with tumor VDR mRNA expression or nuclear immunoreactivity.

Conclusions: Three *VDR* methylation profiles were associated with distinct pACT clinical features and outcome. High VDR methylation was associated with worst outcome. Fully functioning VDR may play a beneficial role against pediatric adrenocortical tumorigenesis. This finding highlights the potential of targeting VDR as an adjuvant therapeutic target.

Reproductive Endocrinology

FEMALE REPRODUCTION: BASIC MECHANISMS

Clinical Case Series of Augmented Fertility in Females After Administration of an Amino Acid Blend That Enhances Release of Human Growth Hormone

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MON-LB003

Supplementation with adjuvant therapies, including growth hormone (hGH), is commonly used to improve fertility treatment outcomes. hGH is important for normal female fertility; low hGH has been associated with causes of infertility and impaired fertility, including polycystic ovarian syndrome (PCOS), endometriosis, diminished ovarian reserve (DOR), and advanced maternal age. A novel, low dose, orally administered amino acid blend has been previously shown in a double-blind, randomized, placebo-controlled, crossover clinical trial to produce a statistically significant increase in endogenous hGH secretion. In this clinical case series, we report outcomes in 7 women with infertility or impaired fertility and conditions associated with low hGH who administered the amino acid blend during fertility treatment (n=5) or timed intercourse/spontaneous pregnancy (n=2). Medical history included conditions associated with impaired fertility and low hGH: endometriosis (n=3), PCOS (n=2), and poor response to ovarian stimulation/history of failed in vitro fertilization (IVF) (n=3). The amino acid blend (containing 2.9 g of L-lysine, L-arginine, oxo-proline, N-acetyl-L-cysteine, L-glutamine, and schizonepeta) was administered daily on an empty stomach. Outcomes included embryo quality and success of embryo transfer (for IVF) and successful pregnancy/live births. Mean±SD age was 33±5 years (range 27-38) and BMI was 27±7 kg/m^2 (range 21-37). Time to pregnancy ranged from 1 week to 9 months (median 3 months) prior to egg retrieval for IVF (n=4),