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5 - EFFECTS OF FIBROBLAST GROWTH FACTOR 21 TO ADRENAL RENEWAL AFTER CHRONIC HYPERCORTISOLISM

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Resumen

After CS is treated, patients develop chronic adrenal insufficiency (AI) and hypothalamus-pituitary-adrenal (HPA) axis dysfunction. Long-term treatment with glucocorticoids (GC) is mandatory to overcome AI. Fibroblast growth factor (FGF21), a key regulator of metabolism, has a bidirectional relationship with GC that bypasses the negative feedback of the HPA axis. In this study, we aimed to investigate the potential effects of FGF21 treatment in the adrenal gland in a mouse model with AI post chronic hypercortisolism. Male mice received corticosterone (CORT) or vehicle (VEH) in the drinking water for 5wks. After this period, the animals developed AI post-CS and were injected daily with recombinant FGF21 for 7d. Plasma circadian and stimulated CORT and ACTH levels were assessed by immunoassay. Adrenal proliferation determined by Ki67 staining. Genes from the liver and adrenal gland were determined by qPCR. During active CS, CORT-treated mice displayed a decreased fasting plasma glucose compared to VEH mice due to basal hyperinsulinemia that maintains even during a glucose challenge. After FGF21 treatment, the AI mice were injected with FGF21, and at 3h they presented a lower ACTH/CORT than the AI-VEH group meaning that their adrenals are more responsive to ACTH. Interestingly, AI-FGF21 mice display higher CORT plasma levels together with higher *Fgf21* liver expression during the circadian cycle than AI-VEH mice. Moreover, the number of proliferating cortical adrenal cells, identified by Ki67 staining, was higher in the AI groups than in CTL groups. In line with this result, AI groups maintained upregulated stem/progenitor markers compared with their respective treatment CTL groups. Interestingly, in hypoglycemic conditions, AI-FGF21 mice presented higher adrenal Sonic hedgehog (Shh) expression levels than CTL-FGF21 and AI-VEH mice. Our data describe that FGF21 contributes to maintaining a sustained CORT secretion and suggests that FGF21 accelerates and supports the adrenocortical cell renewal during AI.