beneficial effects of exercise that is recommended in treatment of both depression and T2DM. Here we compared the effects of ucOCN or exercise in female C57-BL/6J mice under two different metabolic conditions. Mice were fed either a high-fat diet (60% calories from fat) to induce T2DM or a control diet (10% calories from fat). Groups of mice were either sedentary or exercised daily by 30 min treadmill running for two months, with or without daily administration of ucOCN (30 ng/g/day). Mice with T2DM displayed depressive behaviours marked by a higher immobile time in tail suspension tests compared to control mice (97±25 n=11 vs 207±9.0 s n=12; t_{21}=4.21, P=0.0004). Exercise and osteocalcin both improved depressive behaviour (137±8 n=12; t_{22}=5.85, P<0.0001 & 127±15 s n=12; t_{22}=4.46, P=0.0002). Anxiety, measured by the elevated-plus maze revealed the mice with T2DM displayed increased anxiety spending less time in the open arms and had a lower ratio of open to closed arm entries than the control group (0.37±0.03 n=10 vs 0.21±0.032 n=11; t_{19}=3.56, P=0.0021). Neither exercise nor osteocalcin improved anxiety in the T2DM mice. The puzzle box test revealed the negative effects of the high-fat diet in problem solving and memory, where the sedentary mice displayed greater latencies to solve each task compared to control mice. Exercised and mice receiving osteocalcin displayed performances comparable to that of the control group. Under normal metabolic conditions (low fat diet), neither osteocalcin nor exercise altered responses in any of the behavioural tests. Together, these results: 1. The effects of osteocalcin on behaviour and cognition are comparable to that of the effects of exercise in female mice with T2DM; 2. Behaviour and cognition did not improve from exercise or osteocalcin in female mice on a low-fat diet.

References: (1) Ferron et al., Bone. 2012 Feb;50(2):568–575. (2) Oury et al., Cell. 2013 Sep 26:155(1):228–241. (3) Liu et al., Horm Metab Res. 2015 Oct;47(11):813–9. (4) Khaledi et al., Acta Diabetol. 2019 June;56(6):631–650.

Adrenal

ADRENAL PHYSIOLOGY AND DISEASE

The Role of Filamin A (FLNA) in the Regulation of Insulin-Like Growth Factor System in Adrenocortical Carcinomas

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Adrenocortical carcinomas (ACCs) are rare endocrine tumors with poor prognosis. They overexpress insulin-like growth factor 2 (IGF2), that drives a proliferative autocrine loop by binding to IGF1R and IR, with molecular dynamics still poorly identified. Although promising, IGF1R/IR-targeted therapies have demonstrated a limited efficacy in clinical trials in ACC patients. The cytoskeleton actin-binding protein filamin A (FLNA) was shown to impair IR and IGF1R signalling in melanoma and neural progenitor cells, respectively. The aims of this study were to test in ACC cells: 1) FLNA involvement in regulating IGF1R and IR expression and signalling; 2) FLNA role in modulating responsiveness to IGF1R and IGFR/IR inhibitors; 3) FLNA expression in ACCs and correlation with IGF system. In ACC cells we found by immunoprecipitation that both IGF1R and IR interacted with FLNA in basal condition, with an increased or decreased FLNA recruitment to IGF1R and to IR, respectively, after IGF2 stimulation. Genetic silencing of FLNA in ACC cell lines H295R and SW13 induced a significant increase of IGF1R expression (1.4- and 2.3-fold, respectively) and a reduction of IR (-85.5±9.1%, p<0.001 and -32±19.1%, respectively, p<0.05), with a downstream effect of increased cell proliferation (130±13.4%, p<0.01 in H295R and 144.3±23.3%, p<0.01 in SW13 cells) accompanied by an enhanced ERK phosphorylation. Accordingly, in ACC primary cultured cells FLNA silencing increased IGF1R levels (2.9-fold) and enhanced IGF2 effects on ERK phosphorylation by 2.2-fold. In addition, FLNA knockdown potentiated the antiproliferative effects of IGF1R/IR inhibitor Linsitinib and IGF1R specific inhibitor NVP-ADW742 in H295R cells and SW13. This key role of FLNA was even more evident in A7/M2 melanoma cell model, since IGF2 and Linsitinib exerted the expected effects on ERK phosphorylation in M2 cells, lacking FLNA, but not in FLNA-expressing counterpart (A7 cells). Finally, western blot analysis showed significantly lower, although variable, FLNA expression in ACCs (n=10) than in adrenocortical adenomas (ACAs) (n=10) (FLNA/GAPDH ratio 0.37±0.38 and 0.90±0.63, respectively, p<0.05). Interestingly, FLNA/IGF1R ratio inversely correlated with ERK phosphorylation status in ACCs (p<0.05) but not in ACA. In conclusion, we demonstrated that low levels of FLNA enhance both IGF2 proliferative effects and IGF1R/IR inhibitors efficacy in ACC cells, suggesting FLNA as a new factor possibly influencing tumor clinical behavior and the response to the therapy with IGF1R/IR-targeted drugs.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

When the Glucocorticoid Receptor Meets the Mineralocorticoid Receptor in the Nucleus of Human Cells

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Adrenal corticosteroids, such as glucocorticoids and mineralocorticoids, are indispensable for mediating response to stress, development, limiting inflammation, and maintaining energy and fluid homeostasis. These hormones exert their actions via binding to two closely related nuclear receptors, the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). The GR has low affinity for corticosteroids, but is expressed in nearly every cell. In contrast, the MR shows a higher affinity for corticosteroids and its expression is largely confined to those tissues where