Glucocorticoids (GCs) are widely used for the treatment of chronic inflammatory conditions (e.g., rheumatoid arthritis). Their use is accompanied by serious side effects such as the metabolic syndrome and hypertension.

A major scientific effort is in place to find so-called “dissociated compounds” that retain the therapeutic anti-inflammatory properties, while lacking the ability to promote unwanted effects.

GCs signal intra-cellularly by many diverse processes, which can be dimer dependent or independent, and which differ between pathways regulating inflammation and metabolism.

Recent work has revealed that a metabolite of corticosterone (B), namely 5α-tetrahydrocorticosterone (5α-THB), has anti-inflammatory properties in vivo without inducing adverse metabolic effects.

**METHODS**

- The ability of 5α-THB to induce phosphorylation of GR serine 211 (m²GR), a key residue in determining GR activity, was studied by Western blotting in the human pulmonary cell line A549, incubated with steroids for 1h.

- To determine mobility of ligand-bound GR, localisation of green fluorescent protein tagged-rat GR (GR-GFP) transfected in the human kidney cell line HEK293 was monitored by fluorescence microscopy.

- Ligand ability to induce translocation was studied in HEK293 cells by gene reporter induction assay, where the reporter luciferase was under control of either a promoter requiring GR dimers (MMTV) or GR multimers (PNGMT) to drive gene expression. Transfected cells were incubated with steroids for 48h.

- Effects of steroids on mRNA levels of the endogenous GC-responsive metabolic gene tyrosine aminotransferase (Tat) were investigated in the mouse hepatoma cell line BWTG3, naturally expressing GR, by qPCR after treatment for 4 to 24 hours.

**RESULTS**

1) 5α-THB does not phosphorylate Ser211GR

Following ligand binding GR becomes hyper-phosphorylated at Ser211. Phosphorylation of this amino-acid has been linked with translocation of GR to the nucleus and trans-activation of endogenous genes and reporters such as MMTV- and PNGMT-Luc.

2) 5α-THB translocates GR slowly to the nucleus

Corticosterone (B) induces complete GR translocation by 24h, while at 24h 5α-THB translocates 82.71±1.5% of GR. This difference may be a reflection of low levels of phosphorylation at Ser211.

**CONCLUSIONS**

- 5α-THB does not activate GR at Ser211 and fails to induce GR dimer/multimer-dependent pathways activated by classical glucocorticoids. This agrees with our previous in vivo findings that this steroid does not influence metabolism unlike conventional glucocorticoids.

- However 5α-THB can bind GR and induce translocation, behaving like a partial agonist to suppress the action of corticosterone.

- In liver, where it is formed mainly in vivo, 5α-THB may therefore attenuate the effects of endogenous glucocorticoids on metabolic processes.