Long-term use of synthetic corticosteroid drugs increases adrenal gland inflammation

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New research by academics at the University of Bristol has found evidence that prolonged treatment of synthetic corticosteroid drugs increases adrenal gland inflammation in response to bacterial infection, an effect that in the long-term can damage adrenal function.

Synthetic corticosteroid drugs are widely prescribed to treat many inflammatory and autoimmune diseases but taking a high dose over a long period of time can cause adverse side effects. Patients undergoing prolonged corticosteroid treatment can also develop adrenal insufficiency, which in rare occasions can lead to adrenal gland failure.

Previous studies have concentrated on studying the long-term effects of corticosteroid treatment on the hypothalamus and pituitary but have not looked at the direct effects that these steroids may have on the adrenal gland.

In this study, published in *Brain, Behavior, and Immunity*, the research team tested the hypothesis that synthetic corticosteroids cause long-term changes in the adrenal gland steroidogenic pathways that are responsible for adrenal suppression.

The research found that the rhythms of glucocorticoid secretions are disrupted following prolonged treatment with synthetic corticosteroid drugs, and that the adrenal steroidogenic pathway is directly affected. Importantly, these changes persist long after discontinuation of the treatment.

The study also showed a pro-inflammatory effect of synthetic glucocorticoids treatment in the adrenal gland. This is an important finding with high clinical relevance as intra-adrenal activation of the immune system can affect adrenal functionality by interfering with the steroidogenic pathway, damaging adrenal endothelial microvascular cells, and by inducing apoptosis and reducing cell viability.

Dr. Francesca Spiga, Honorary Research Fellow in the Bristol Medical School: Translational Health Sciences (THS) and corresponding author, said: "Our study provides valuable insights on the regulation of the adrenal steroidogenic pathway that are important starting points for

future studies on adrenal gland physiology.

"Importantly, our research builds on our knowledge of the mechanisms through which corticosteroid drugs induce adrenal insufficiency, by showing simultaneous effects within multiple pathways involved in steroidogenesis, including circadian clock genes and inflammation pathways.

"A more detailed understanding of the effects of synthetic glucocorticoids on glucocorticoid hormone's dynamics and on adrenal steroidogenic activity and the identification of mechanisms regulating these effects, will help develop better treatments that will improve patient care."

Future studies should address whether adrenal insufficiency, and its effects, can be prevented by using synthetic corticosteroid drugs that more closely resemble endogenous glucocorticoids in term of effectiveness and plasma half-life.

Endogenous glucocorticoids (cortisol in humans, corticosterone in rodents) regulate many physiological functions, including metabolism, cardiovascular tone, reproduction, mood and cognition, and the immune system. Clinical therapy with high doses of synthetic corticosteroids results in adrenal insufficiency, characterised by adrenal atrophy and decreased basal and stress-induced cortisol secretion, that may persist for several years after therapy withdrawal. One of the pathological consequences of adrenal insufficiency is the potential development of an adrenal crisis resulting from decreased cortisol secretion in response to inflammatory stressors such as infections, injuries and major surgery.

More information: Francesca Spiga et al. Prolonged treatment with the synthetic glucocorticoid methylprednisolone affects adrenal steroidogenic function and response to inflammatory stress in the rat.

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