Selective Glucocorticoid Receptor Modulators: Future of Glucocorticoid Immunosuppressive Therapy?

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In 1950 Hench, Kendall, and Reichstein received the Nobel Prize in Medicine for the characterization and isolation of glucocorticoids and the subsequent discovery of their anti-inflammatory properties. To date, glucocorticoids are still widely prescribed and play an important role in the treatment of a variety of clinical disorders, including inflammatory diseases, autoimmune disorders, and hematological malignancies, as well as in the prevention of allograft rejection. Chronic glucocorticoid treatment is, however, associated with serious side effects like weight gain, hypertension, diabetes mellitus, osteoporosis, etc. In patients with Cushing’s disease, chronic (endogenous) hypercortisolism often leads to irreversible changes in body composition (1, 2) and appears to be associated with an impaired quality of life (3) and an increased cardiovascular morbidity and mortality (4, 5). Therefore, patients who are chronically exposed to supra-physiological dosages of glucocorticoids are likely to be at risk for the same complications as patients with Cushing’s disease. This highlights the importance of development of glucocorticoid receptor (GR) targeting compounds with selective immunosuppressive properties but with fewer metabolic side effects.

Insight in the mechanism of action of glucocorticoids and the GR has led to the development of selective GR modulators (SGRM) (6–10). Glucocorticoids readily diffuse across the cell membrane and bind to the GR. Upon binding of glucocorticoids, the ligand-receptor complex migrates toward the nucleus, where it can up- or down-regulate the expression of target genes (7, 11–13). The first mode of transcriptional regulation requires binding of the liganded dimerized GR on glucocorticoid-responsive elements, ideally a palindromic 15-bp sequence (5’-GGTACAnnnTGTTCT-3’). The intrinsic histone acetyltransferase activity of recruited coactivators promotes remodeling of the chromatin and stimulates initiation of transcription by the RNA-polymerase II complex (14, 15). This process of genes that are transcribed at higher rates upon binding of the liganded GR-complex on glucocorticoid-responsive elements is called transactivation. Several transactivated genes have been implicated as key players in the pathogenesis of several side effects of glucocorticoids like hyperglycemia, adipogenesis, and muscle wasting (16, 17).

The second mechanism of transcriptional regulation acts by interference of the GR-monomer with other transcription factors and is independent of dimerization and DNA binding. Transrepression of proinflammatory modulators as nuclear factor κB and AP-1 inhibits the downstream inflammatory cascade and is traditionally considered to be the predominant mechanism regulating anti-inflammatory actions of glucocorticoids (11–13).

In the past decade, several steroidal and nonsteroidal SGRM have been developed with dissociated effects on gene expression, favoring transrepression over transactivation, thereby aiming to reduce transactivation-related side effects (6–10). However, these compounds have not reached the clinic yet for several reasons, including lack of efficacy in vivo and/or insufficient dissociative capacity. In this issue of Endocrinology, Hu et al. show that a series of new selective tricyclic modulators of the GR retains immunosuppressive effects, whereas the effects on transactivation range from partial agonistic to fully antagonistic. Interestingly, angular benzyl tricyclic GR ligands with full antagonistic properties for reporter gene activation inhibited IL-6 production in vitro to levels that were at least 70% of the inhibition level of prednisolone. In line with these observations, full antagonist compounds were able to suppress lipopolysaccharide-stim-
ulated interferon-γ production in whole-blood assays and, even more important, were proven to have antiinflammatory properties in vivo using the lipopolysaccharide-induced endotoxemia mouse model.

Compared with the partial agonistic compounds, full antagonistic compounds did not induce adipocyte differentiation and induced to a lesser extent expression of enzymes involved in gluconeogenesis [PEPCK (phosphoenolpyruvate) and TAT (tyrosine aminotransferase)]. In addition, normal levels of osteocalcin were secreted by osteoblasts after treatment with the full antagonistic compounds, pointing toward reduced effects on the bone matrix. This has also been shown for the SGRM compound A, which suppresses proinflammatory cytokine production in vitro without any inhibitory effect on osteoblast differentiation in vitro or in vivo (18). Finally, it was shown that the partial agonistic activity of the full antagonistic compounds on gluconeogenesis enzyme expression levels may be related to the tissue level of the coactivator PGC1α.

Altogether, these are promising results that justify further investigation of these new dissociated GR agonists. There are, however, several points of concern that need to be addressed before these compounds can be translated into clinical practice. First, additional in vivo studies are needed to examine the dissociative capacity of these compounds in terms of sufficient immunosuppressive potential (adequate transrepression) without occurrence of specific side effects (no or attenuated transactivation) and whether concentrations that are effective in vitro can be reached in vivo. It should in particular be evaluated whether the transactivating effects of the full antagonistic SGRM on enzyme expression of the gluconeogenesis pathway can disturb glucose tolerance in vivo. In addition, the effects of long-term treatment with these compounds on adipogenesis, bone formation, and muscle protein catabolism should be investigated.

Second, the safety of sustained SGRM-mediated antagonism of gene expression controlled by transactivation needs to be examined. Blockade of transactivation might interfere with glucocorticoid-mediated responses in physical stress conditions (7), e.g. up-regulation of adrenergic receptor expression. In addition, several immunosuppressive effects of glucocorticoids are not mediated by transrepression but via transactivation of antiinflammatory genes. Examples are the genes encoding for glucocorticoid-induced leucine zipper, which inhibits inflammatory transcription factors (19), and mitogen-activated kinase phosphatase-1, which suppresses inflammatory gene expression via inhibition of MAPK signaling pathways (20). The effects of SGRM on expression of these antiinflammatory genes clearly needs further investigation.

Third, glucocorticoid resistance is present in up to 30% of patients with rheumatoid arthritis (RA), inflammatory bowel disease, and asthma (21–23), and for clinical practice, it would be highly relevant to know whether SGRM are more efficacious than traditional glucocorticoids to overcome glucocorticoid resistance without otherwise inevitable side effects.

In this perspective, it should be emphasized that innovation of glucocorticoid therapy should not only include development of SGRM but also the development of tools to assess individual glucocorticoid sensitivity to achieve customized treatment. Glucocorticoid sensitivity is influenced by both genetic and acquired factors. We previously showed that polymorphisms of the GR gene that lead to relative glucocorticoid resistance are associated with an increased risk to develop RA and also with a more aggressive disease phenotype (24). Acquired, inflammation-related factors that influence glucocorticoid sensitivity involve proinflammatory cytokines that induce glucocorticoid resistance at the site of inflammation via several mechanisms (reviewed in Refs. 25, 26), like reduction of GR number and affinity, impairment of GR function, and induction of the GR splice variant GRβ, which may be a dominant-negative inhibitor of the wild-type GR. Furthermore, cytokines may decrease cellular glucocorticoid availability by up-regulation of the multidrug resistance gene MDR1 that encodes the P-glycoprotein multidrug efflux pump that can transport glucocorticoids out of cells (25, 26).

Preliminary studies show that measurement of GR number, GRβ expression, and MDR1 expression by peripheral blood mononuclear cells (PBMC) may predict the response to glucocorticoid treatment (25, 26). In this respect, bioassays, measuring responses of PBMC to glucocorticoids in vitro, may also be useful as has been shown in inflammatory bowel disease and asthma (27, 28). Using a recently developed bioassay measuring dexamethasone-mediated transrepression (via IL-2 expression) and transactivation (via glucocorticoid-induced leucine zipper expression) in PBMC (29), we found that cellular GC sensitivity in vitro is correlated with the clinical response after short-term glucocorticoid treatment in patients with RA (our unpublished data). Future studies are needed to optimize assessment of individual glucocorticoid sensitivity with several (combined) tools, allowing for tailor-made therapy with glucocorticoids or SGRM. In addition, other therapeutic strategies should be explored that can increase glucocorticoid sensitivity, e.g. via compounds that inhibit inflammatory transcription factors (e.g. nuclear factor κB, AP-1), MAPK, and MDR-1.

In conclusion, the findings of Hu et al. (30) open further perspectives for the development of new SGRM that couple potent immunosuppression to a reduced side-effect profile. Dissociation of GC-induced side effects from the immunosuppressive effects of GC by modulating the balance in favor
of transrepression would certainly be a major step forward in clinical medicine. Clearly, extensive studies are needed to evaluate long-term efficacy and safety in various conditions. In addition, innovation of glucocorticoid immunosuppression therapy should also be directed to improve assessment of glucocorticoid sensitivity and to develop therapeutic strategies that reduce glucocorticoid resistance.

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References