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A proteomic investigation into mechanisms underpinning corticosteroid effects on neural stem cells

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Highlights

- Treatment of NSCs with a widely used clinical corticosteroid showed that proliferation of neural stem cells was reduced.

- Genesis of neurons and axonal length were reduced, while oligodendrocyte maturation was increased after corticosteroid treatment.

- Proteomic analysis shows corticosteroids induced downregulation of GAP-43 and MMP-16 with upregulation of CYP51A1.

Abstract

Corticosteroids (CSs) are widely used clinically, for example in pediatric respiratory distress syndrome, and immunosuppression to prevent rejection of stem cell transplant populations in neural cell therapy. However, such treatment can be associated with adverse effects such as impaired neurogenesis and myelination, and increased risk of cerebral palsy. There is increasing evidence that CSs can adversely influence key biological properties of neural stem cells (NSCs) but the molecular mechanisms underpinning such effects are largely unknown. This is an important issue to address given the key roles NSCs play during brain development and as transplant cells for regenerative neurology. Here, we describe the use of label-free

quantitative proteomics in conjunction with histological analyses to study CS effects on NSCs at the cellular and molecular levels, following treatment with methylprednisolone (MPRED). Immunocytochemical staining showed that both parent NSCs and newly generated daughter cells expressed the glucocorticoid receptor, with nuclear localisation of the receptor induced by MPRED treatment. MPRED markedly decreased NSC proliferation and neuronal differentiation while accelerating the maturation of oligodendrocytes, without concomitant effects on cell viability and apoptosis. Parallel proteomic analysis revealed that MPRED induced downregulation of growth associated protein 43 and matrix metallopeptidase 16 with upregulation of the cytochrome P450 family 51 subfamily A member 1. Our findings support the hypothesis that some neurological deficits associated with CS use may be mediated via effects on NSCs, and highlight putative target mechanisms underpinning such effects.

Abbreviations

CS, corticosteroid; CNS, central nervous system; NSCs, neural stem cells; SCI, spinal cord injury; MPRED, methylprednisolone; NPCs, endogenous neural progenitor cells; FGF2, human recombinant basic fibroblast growth factor; EGF, epidermal growth factor; TUJ 1, neuron specific class III β-tubulin; GFAP, glial fibrillary acidic protein; MBP, myelin basic protein; DAPI, 4′, 6-diamidino-2-phenylindole; Ambic, Ammonium Bicarbonate; SVZ, subventricular zone; DMEM, Dulbecco's Modified Eagle Medium; DMSO, dimethyl sulfoxide; PBS, phosphate buffered saline; PFA, paraformaldehyde; RT, room temperature; Edu, 5-ethynyl-2′-deoxyuridine; FBS, fetal bovine serum; IPA, Ingenuity Pathway Analysis; GRs, glucocorticoid receptors; MMP-16, matrix metallopeptidase-16; GAP-43, growth associated protein 43; CYP51A1, cytochrome P450 family 51 subfamily A member 1; ECM, extracellular matrix; OPCs, oligodendrocyte precursor cells

Keywords

Corticosteroid; Neural stem cell; Neural cell; Proteomics

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