Proof of concept for a newly identified target, 11-beta-hydroxysteroiddehydrogenase type 2, to treat therapy refractory depression – the effect of glycyrrhizin on treatment outcome

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Abstract

Background: Mineralocorticoid receptor (MR) dysfunction has been linked to therapy refractoriness in patients with major depression (1). This may be based on a primary alteration of the MR or of the regulation of its primary ligands aldosterone or cortisol (2). We identified markers of MR function, which appear to predict treatment outcome of hospitalized patients, who were treated with standard medication for depression. These were most consistently low systolic blood pressure and a high salivary aldosterone/cortisol ratio. This pattern points to a peripheral MR dysfunction and a reactive increase in aldosterone secretion. In addition, these markers appear to be stable over the course of depression, i.e. are rather trait- than state markers (3). Aldosterone appears to act specifically on selected brain areas, which are involved in autonomic and mood regulation, in particular the nucleus of the solitary tract, the amygdala and others.

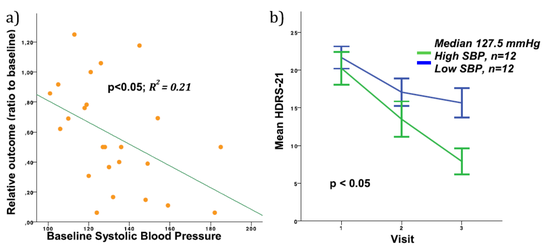
Aims and Objectives: We hypothesized that a reversal of these markers, i.e. the lowering aldosterone and at the same time an increase systolic blood pressure could reverse therapy refractoriness. We identified a molecular target, the 11-beta-hydroxyteroid-dehydrogenase type 2 (11-beta-HSD-2), and a model compound, which inhibits its activity, i.e. glycyrrhizin as main constituent of glycyrrhiza glabra (GLZ), with the envisioned property.

Methods: We administered an extract in the form of capsules from an extract of Glycyrrhiza glabra (GLZ) containing 7-8 % of glycyrrhizin in a dose of 2 x 700 mg daily adjunct to hospitalized patients with major depression, who were treated with standard antidepressants. Clinical and biomarker assessments were done at baseline and approximately 2 weeks and 6 weeks after baseline.

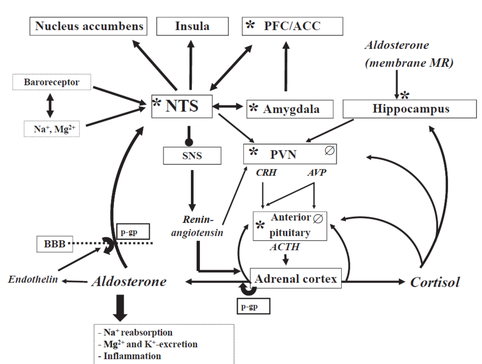
Results:12 subjects were treated with GLZ and compared to 55 subjects, who were treated with standard of care only, in an open label fashion. In the GLZ group, blood pressure increased slightly, whereas it dropped in the treatment as usual group, indication target engagement. After two weeks of treatment the primary outcome variable, the Hamilton-Depression Rating Scale (HAMD-21) change from baseline differed significantly between the groups ($p < 0.05$), indicating a therapeutic benefit of GLZ. In addition, the global assessment of function and the CGI-S showed a significant improvement in patients treated with GLZ in comparison to standard treated patients (both $p < 0.05$). Six of the 12 patients where released from the hospital between week 2 and 6. This supports clinical efficacy, but also made the week 6 assessment not valid.

Discussion and Conclusion: Alterations in autonomic and neuroendocrine control appears to affect treatment response in patients with depression. The combination of high aldosterone and low blood pressure values appears to indicate such a risk. The enzyme 11-beta-HSD-2 appears to be a target to overcome this.

Context

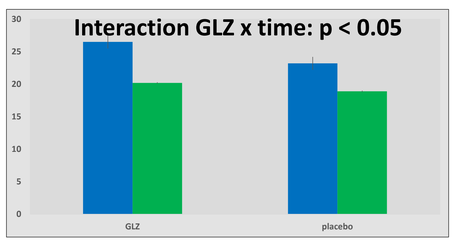


Systolic blood pressure predicts improvement of depression in hopsitalized patients treated with standard therapy (2)



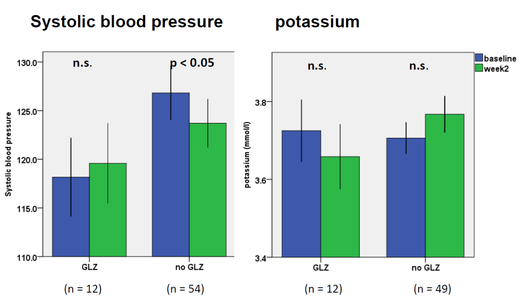
Behaviorally relevant targets for aldosterone action in the brain (1)

Results



(n = 12) (n = 55)

HAMD-21 change in the GLZ vs placebo (baseline to week 2)



Biomarker changes with GLZ adjunct treatment vs. standart of care.

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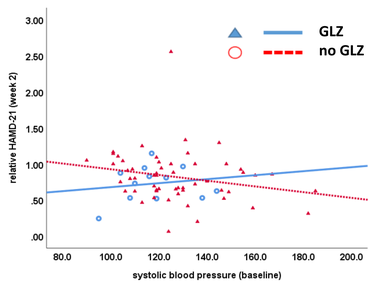

Preferential differentiation in patients with lower blood pressure.

Conclusion

GLZ may have antidepressant properties by overcoming a biomarker constellation, which appears to determine therapy refractoriness. As the primary action of the GLZ constituent glycyrrhizin is to inhibit 11-beta-HSD2, this principal may emerge as a new target for a subgroup of patients with depression,

References

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3. Murck H, Braunisch MC, Konrad C, Jezova D, Kircher T (2019): Markers of mineralocorticoid receptor function: changes over time and relationship to response in patients with major depression. Int Clin Psychopharmacol. 34:18-26.

Acknowledgement:

We thank Gall Pharma, Austria, for providing Glycyrrhiza glabra extract capsules.