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# Discovery of Personalized Treatment for Immune-Metabolic Depression—Focus on 11beta Hydroxysteroid Dehydrogenase Type 2 (11betaHSD2) and Toll Like Receptor 4 (TLR4) Inhibition with Enoxolone

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Review

# Discovery of Personalized Treatment for Immune-Metabolic Depression—Focus on 11beta Hydroxysteroid Dehydrogenase Type 2 (11betaHSD2) and Toll Like Receptor 4 (TLR4) Inhibition with Enoxolone

**Short Title:** Treatment of immune-metabolic depression

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## Abstract

Treatment options for major depression are limited: only about 1/3 of patients achieve remission with first line treatments. More importantly; there are no established predictive markers to identify patients who may be treatment refractory. Research from us and others have established markers related to metabolic disturbances (increased BMI; increased triglyceride levels); inflammatory markers (C-reactive protein; CRP); autonomic disturbances (reduced blood pressure; reduced heart rate variability); brain morphology changes (increased volume of the choroid plexus and brain ventricle volumes). Approximately 1/3 of patients with depression may express these characteristics. These features can mechanistically be linked to a reduced sensitivity of peripheral mineralocorticoid receptors and as a consequence increased release of renin from the kidney; increased production of angiotensin and increased adrenal release of aldosterone. The primary CNS target of aldosterone is a key center of autonomic and affect regulation; i.e., the nucleus of the solitary tract (NTS); which is also the entry point of the vagus nerve; which provides signals from baroreceptors and chemoreceptors. In search of a mechanism to overcome this pathology we identified a molecule; which is derived from the licorice plant glycyrrhiza glabra; namely glycyrrhizin and its biologically active metabolite enoxolone. These molecules have been demonstrated to reverse some of these markers by a well understood dual mechanism: It inhibits the enzyme 11beta hydroxysteroid-dehydrogenase type 2 (11betaHSD2) and inhibits the toll like receptor 4 (TLR4); i.e., the ligand for lipopolysaccharide (LPS) and trigger of innate immunity. As a consequence; patients which show an increase in inflammation markers; an increase in aldosterone or a low blood pressure; are a preferential target population for this compound. Importantly; these patients can be identified as likely treatment refractory BEFORE a treatment is initiated. Clinically; these patients are primarily young females or patients with a history of childhood trauma. A combination of enoxolone with standard antidepressants may therefore avoid a trial and error approach in these subjects and will benefit them by achieving recovery faster.

**Keywords:** autonomic nervous system; sympathetic; parasympathetic; vagus; blood pressure; baroreceptor; nucleus of the solitary tract; area postrema; aldosterone; cortisol; 11beta hydroxysteroid-dehydrogenase type 2; toll like receptor 4 (TLR4); glycyrrhizin; glycyrrhetic acid; enoxolone; therapy refractory depression; neuroinflammation

## Introduction

STAR-D, a large open label study in patients with depression revealed that first line treatment with the standard antidepressant, sertraline, a selective serotonin reuptake inhibitor (SSRI) leads to remission on only approx. 30% of patients [1]. Apparently, standard antidepressants only work for a small subgroup of patients with depression. Established markers to identify these subjects do not exist, but a number of important demographic, clinical and biomarker characteristics have been reported.

A well characterized clinical differentiation may help with the identification of biological subtypes of more difficult to treat patients. That is the distinction between melancholic and atypical depression. Atypical depression vs. other forms is associated with worse treatment outcome [2,3]. Atypical depression shows hypersomnia, hyperphagia, emotional irritability and somatic complaints [4].

Melancholic depression shows largely opposite features, including weight- and appetite loss, early morning awakening, psychomotor changes and a specific melancholic mood, sometimes referred to as “feeling of feelinglessness”. Differential biological pathways underlie these subtypes, which involve endocrine regulation (HPA-axis and renin-angiotensin-aldosterone system [RAAS]), metabolic status, and autonomic characteristics, including blood pressure and inflammation parameters [4–7]. Atypical depression has been recognized as a form, which goes along with a reduced noradrenergic activity and normal to reduced cortisol plasma concentration [8,9], whereas an increase in HPA axis activity and noradrenergic activity is related to melancholia.

Despite the fact that melancholic depression is the textbook form of this disorder, it appears to contrast with the foundational neurobiological explanation of the neurobiology of depression, i.e., the idea of a monoamine deficit in depression. This hypothesis was based on the efficacy of norepinephrine reuptake- and monoamine oxidase- inhibitors [8] and the observation that reserpine, a compound which depletes noradrenaline, induces depression [10]. Interestingly, reserpine was utilized as a medication to treat hypertension, i.e., to lower blood pressure, with one important adverse event: fatigue. In accordance some studies reported reduced sympathetic activity was reported in patients with clinical depression [11–13], as assessed with electrodermal skin conductance determination. In contrast, increased muscle sympathetic nervous activity (MSNA) was observed in severely depressed patients, who are often melancholic, compared to controls, and MSNA correlated with the severity of depression in these subjects. Interestingly, MSNA could be reduced by the treatment with the SSRI sertraline [14]. Major depression, which is associated with increased sympathetic nervous system activity can therefore go along with arterial hypertension [15] and, as outlined below, may respond better to standard antidepressants.

Several newer studies revealed a number of additional differentiating characteristics between atypical and melancholic depression, namely an increase in inflammation and metabolic characteristics, including an increase in body mass index (BMI) and triglyceride levels in the atypical form [16–18]. Interestingly, autonomic markers, including higher heart rate and low cardio-autonomic balance (derived from respiratory sinus arrhythmia and pre-ejection period; higher values are associated with higher parasympathetic activity) where predictive of lower low density lipoprotein (LDL) two years later, indicating that metabolic changes are consequences of autonomic vulnerability factors [19].

On that basis a framework of immune-metabolic depression was developed, which shows an overlap with atypical depression symptoms. Of importance, the context of these biomarkers may be of importance: for example elderly men, who are often melancholic, show an increase in inflammation, which may be related to a different mechanism than in young women [20], who preferentially show signs of atypical depression (see below). We will focus on the relevant biomarkers in the following, starting with a simple biomarker, blood pressure.

## Blood Pressure

The fact that patients with depression have rather a low vs. high blood pressure is well established [21,22]. This study of Licht et al., also demonstrated that standard antidepressants tend to increase blood pressure. Similarly, anxiety and depression were associated with low blood pressure in several large studies [23,24] including in elderly subjects [25]. Additional features of low blood pressure are fatigue or hypersomnia: this has parallels to chronic fatigue syndrome (earlier referred to as neurasthenia) [26,27]. Vice versa, higher blood pressure is linked with lesser perceived stress and higher quality of life [28–30]. On the basis of the observation of an inverse relationship of blood pressure and wellbeing, Dworkin formulated the hypothesis of “learned hypertension”, i.e., blood pressure is upregulated based on the sense of an improved wellbeing [31]. This hypothesis was largely confirmed on the basis of long term data [32].

Blood pressure has only recently been a focus of interest as predictors of depression development, i.e., as a vulnerability marker: Low blood pressure is associated with an increased risk to develop depression [33] and in particular for atypical depression, but appears to be protective against melancholic depression [34]. Low blood pressure is also a risk factor for therapy non-response in depression [35], primarily in women [36]. This is supported by data comparing outpatients with hospitalized patients with depression, the latter plausibly with more refractory forms, which show a reduced blood pressure in comparison to outpatients [37] despite the fact that waist-hip ratio and lipid levels were also higher in this population [37]. In addition, these subjects showed high triglycerides and low HDL. These additional parameters may have contributed to the assumed therapy refractoriness.

Dynamic changes of blood pressure in the course of the day should also be considered. A drop of more than 10 % of systolic blood pressure during sleep defines a so called dipper status, which is associated with lower cardiovascular risk in comparison to non-dippers. Non-dipper status is often observed in patients with hypertension, who also show higher anxiety and depression levels [38], sleep disturbance [39], or shorter sleep duration [40]. However, one study found a more pronounced blood pressure dip [41] in patients with higher depression severity. Use of sedating medications in the study population was made responsible for that.

Support for a causal relationship between low blood pressure and depressed mood and not only an association is implied by observations that pharmacological interventions with the alpha adrenergic compound midodrine [42], increased salt intake or the MR agonist fludrocortisone improve orthostatic reactions [43] and depressive symptoms [44,45]. Influences of vagal function can be suggested from findings in patients with vasovagal syncope, who did not respond to pharmacological or non-pharmacological treatment [44]. These patients showed higher depression and anxiety ratings; even subsyndromal orthostatic hypotension is associated with cognitive dysfunction, increased hopelessness [46] and increased risk of anxiety and depression [47].

## Renin-Angiotensin Aldosterone System:

Aldosterone is a steroid hormone best known for its blood pressure regulating effect. It is regulated via the sympathetic nervous system by beta adrenergic activation of the renin-angiotensin II cascade; in addition in the short term the HPA axis is involved, as ACTH also leads to aldosterone release (see [48]). Potassium can directly release aldosterone from the adrenal cortex. Mineralocorticoids, including aldosterone, have been recognized to affect brain function, focusing on autonomic, not emotional regulation [49]. This is despite the fact the Selye, who brought the “stress” concept into neurobiology, pointed out the importance of mineralocorticoid, like aldosterone as a stress hormone [50]. Selye already identified the proinflammatory effect of mineralocorticoids. Only more recently was aldosterone’s role in emotional regulation recognized [35,48,51–53] and its pro-inflammatory role further supported [54].

The role of aldosterone as a mediator to induce depression was established: acute stress and experimental models of depression, including tryptophan depletion and magnesium-depletion, lead

to an increase in plasma aldosterone in animal models [55–57]. This points to an involvement of glutamatergic and serotonergic mechanisms. Acute stress also leads to an increase in aldosterone in healthy volunteers [58,59].

The fact of an increased level of aldosterone in patients with depression is now well established [60–64]. A causal relationship is implied by the observation that aldosterone leads to depressive and anxiety symptoms, as for example demonstrated in patients with primary hyperaldosteronism, and symptoms improve after its treatment [65,66]. Besides depression and anxiety, somatic complaints are common in these patients. Also, animal data show that subchronic infusion of aldosterone leads to depression and anxiety like behavior [51]. Similarly, polymorphisms of the renin-angiotensin aldosterone system, i.e., of the angiotensin converting enzyme (ACE) and the angiotensin II (ATII) receptor are associated with worse treatment outcome for the more biologically active genotypes [67]. Important in our context, a high ratio of saliva aldosterone/cortisol appears to be related to lesser therapy response [35] in hospitalized patients with depression.

Of note, the increase in aldosterone as observed with an aldosterone releasing adenoma or aldosterone administration is associated with an increase in blood pressure and increased BMI. Increased BMI and increase aldosterone/renin ratio were positively, but independently associated with the severity of depression symptoms [68]. Interestingly, in the latter study an increase in blood pressure was associated with less anxiety in men, which may point to a counterregulatory mechanism of blood pressure on anxiety, possibly via baroreceptor activation (see below). This is in also in line with the above described protective effect of a higher blood pressure against the development of depression.

What is the mechanism of aldosterone to induce depression? Aldosterone has a fairly specific neuronal target, i.e., nucleus of the solitary tract (NTS). The NTS regulates autonomic function, as outlined below, an projects to anatomical targets related to motivation, like the nucleus accumbens; interoception, like the insula; as well as prefrontal cortical areas, like the anterior cingulate [69–71]. Specifically, aldosterone acts at neurons, which co-express MR and the enzyme 11-beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2). This enzyme rapidly degrades cortisol intracellularly and therefore lets aldosterone to compete at the MR, which otherwise would be occupied with the much higher concentrated cortisol. In the absence of 11betaHSD2, as for example in the hippocampus, cortisol/corticosterone is the main ligand at the MR. These neurons of the NTS, which co-express MR and 11beta HSD2, overlap with those of vagus nerve afferents [72] and are involved in salt appetite [73]. This is relevant as salt appetite is increased in depression and anxiety [74–76] and can be used as a behavioral marker for central MR activation. The NTS is also activated via the baroreceptor, which indirectly inhibits sympathetic neurons in the rostroventrolateral medulla (RVLM) [77]. At the same time baroreceptor activation increases parasympathetic output. Aldosterone inhibits this mechanism [78], therefore activating the sympathetic and inhibiting the parasympathetic nervous system. Interestingly, baroreceptor activation may induce an anti-inflammatory action [79], which will be covered later. Another nucleus which may be involved in sympathetic regulation of aldosterone is the paraventricular nucleus of the hypothalamus, which, similar to the NTS, coexpresses 11betaHSD2 and MR. Inhibition of 11betaHSD2 leads to an activation of the PVN, which goes along with an increase in HPA axis activity, an increase in blood pressure as well as an increase in renal sympathetic activity [80]. In contrast to the area postrema/NTS complex, this nucleus is protected by the blood brain barrier, which may dampen the effect of aldosterone at this nucleus.

## What Leads to an Increase in Aldosterone?

Aldosterone release is activated by low blood pressure (via RAAS activation) and low plasma sodium. The low blood pressure as a trigger needs to be explored. One potential explanation is that lower blood pressure is related to lower peripheral mineralocorticoid receptor (MR) sensitivity: we observed evidence for that in our study [35], as the correlation curve between aldosterone and blood pressure was shifted to the right in non-responders to standard treatment, i.e., a higher aldosterone

concentration is required to maintain the same blood pressure. A kidney related mechanism for this appears plausible, as a reduced MR sensitivity at the kidney leads to a reduced sodium reuptake. Alternatively, a vascular mechanism could be involved, similarly to what was proposed in patients with joint hypermobility and reduced vascular tone [81]. The same conclusion of a reduced peripheral MR activity was drawn based on neuroendocrine challenge experiments with a mixed MR-GR agonist [82,83]. In line with this, the adjunct administration of the MR agonist fludrocortisone lead to a faster clinical response to standard antidepressants in comparison to placebo [45]. At the same time, fludrocortisone reduces aldosterone plasma levels. This is most likely a peripheral phenomenon, as fludrocortisone crosses the blood brain barrier only in a very limited way [84].

A consequence of this is the activation of a compensatory mechanism: aldosterone and other MR agonists increase salt intake [85,86] Accordingly, MR antagonists reduce appetite for salt ([87,88]. Patients suffering from depression often suffer from loss of appetite, which could be caused by a subjective tastelessness of food, based on an increased salt taste threshold and increased salt preference [35]. This mechanism can be induced by salt restriction, which leads to an increase in aldosterone and as a consequence an increase in inflammation markers and metabolic markers, including triglycerides, as demonstrated in a large meta analysis [89]. Salt restriction also leads to increased signs of depression and anxiety in animal models [90,91] and in epidemiological studies [92]. In addition and already mentioned above, serotonergic [56,93,94] and glutamatergic mechanisms [57] play a role.

A link to sleep may exist: there is a close temporal relationship between the activity of RAAS and sleep processes: the concentration of renin and aldosterone increases in synchrony with an increase in SWS [95]. Thus, the total sleep duration as well as the duration of SWS provides a possible correlate for the activity of the MR. On the other hand, conditions with sleep disturbances also show increased nightly aldosterone concentrations. These include major depression (see above) as well as obstructive sleep apnea [96] and prolonged physical strain [97].

## Inflammation

Inflammation has long been described as a component of major depression [98]. Higher levels of inflammation are linked to treatment resistance to standard antidepressants [17,99]. In depressed patients, inflammatory changes are found including of CRP and IL-6, slightly less expressed change also takes place with IL-1 [100,101]. The pathophysiology of inflammation in depression is an area of active research.

One important trigger of inflammation is the activation of the toll like receptor 4 (TLR4), which leads to the release of inflammatory cytokines. The TLR4 is the receptor for lipopolysaccharide (LPS, endotoxin). An increased brain expression of TLR4 has been observed in a broad range of neuropsychiatric disturbances, including major depression [102].

Peripheral administration of LPS is an established model for depression in animal models [103–105] and induces depressive symptoms in humans [106]. Increased LPS levels are associated with some forms of depression [107], possible based on a “leaky gut” , which may be the consequence of autonomic dysregulation.

TLR4 receptors are regulated by a range of relevant signal pathways, including the beta adrenergic [108], act synergistically with NMDA receptor blockade to reduce white matter integrity [109] and influence the anti-inflammatory and neuroprotective role of glucocorticoids by acting on microglia [110]. Importantly, psychological stress is able to induce TLR4 expression. [111–113]. This leads to an increase in the expression of proinflammatory factors interleukin 1beta (IL1b), cyclooxygenase 2 (COX-2) and prostaglandin E2 (PGE2) in the brain cortex and is associated with an increase in depression related behavior as assessed in the forced swim test [113]. An activation of the nuclear factor kappa B (NFkB) inflammatory pathway was involved [114]. Blocking TLR4 receptors pharmacologically prevented an increase in TLR4 expression within the prefrontal cortex of rats [115]. Bacterial translocation from the gut may be involved in this mechanism, as implied by a suppression of this reaction by antibiotics. This action may involve monocytes and brain macrophages

[116,117]. Intracerebroventricular administration of LPS leads to an increase of the expression of TLR4 at ventricular ependyma, the choroid plexus and the area postrema [117], which may lead to a feed forward cycle.

A CNS pathway has been described, which regulates peripheral inflammatory activity, i.e., the neuroimmune reflex [118,119]: inflammatory signals from the periphery are transmitted via vagal afferents to the NTS, which then leads to an activation of vagal efferents to the spleen. This vagal activity suppresses inflammatory activity, creating a feedback loop! Therefore, the key anatomical target for aldosterone is involved in the regulation of inflammation. Supporting the physiological relevance, TLR4 is expressed in astrocytes of the area postrema and NTS, i.e., the main targets for aldosterone! The involvement of astrocytes links its mechanism to the glutamatergic system [120], which is the main transmitter of the afferent vagus nerve [121]. Disturbances not only of autonomic regulation, but also interoception can be expected [71], which is reflected in the typical somatoform complaints of patients with increased inflammatory activity.

In our context the anatomical locations of TLR4 are of interest in order to identify these receptors as treatment targets. The TLR4 is expressed in astrocytes of the choroid plexus, circumventricular organs including the area postrema and the nucleus of the solitary tract [122] as well as in the nodose ganglion of the vagus nerve [123]. This makes these TLR4 receptors accessible for systemic treatments without the need to cross the blood brain barrier! Of note, the area postrema is closely connected to the NTS, the primary target for aldosterone. This is a remarkable coincidence for the mode of action of our identified intervention (see below) that the main anatomical area for aldosterone is also affected by TLR4. It shows the synergism between both the RAAS and inflammation on a physiological level. This finding has a major relevance for the treatment approach, which will be described later. A further synergism at a molecular level exists, which will be covered in the next section.

The close link between autonomic nervous system and inflammation was outlined recently with the overall perspective that activation of the SNS is proinflammatory in nature and related to reduced vagal/parasympathetic function) [124] [125]. However, in later stages of a disease process, an increase in SNS activity may be beneficial [126].

## RAAS and Inflammation

Aldosterone is related to inflammatory and metabolic disturbances [127] [128] an correlation was seen to an increase in CRP, insulin, total cholesterol, triglycerides in young obese adults. As mentioned already a physiological interaction between aldosterone and inflammation exists via aldosterone's action on the NTS. On a molecular level aldosterone acts synergistically at the trigger for the innate immunity, the toll like receptor 4 (TLR4) receptor [129]; furthermore, TLR4 activation by lipopolysaccharide (LPS) induces aldosterone release and inflammation at the adrenal cortex, which can be suppressed by an inhibitor of the RAAS, i.e., an angiotensin II (ATII) receptor antagonist [130]. This may create a feed forward cycle. Indeed, the proinflammatory effect of ATII and its potential role in depression is well established [131].

A direct effect of aldosterone to induce inflammation has been reported: aldosterone acts on neutrophils: the neutrophil/lymphocyte ratio is correlated with aldosterone plasma concentration in patients with primary hyperaldosteronism [132]. Aldosterone induces Th17 cells [133,134] and Th17 cells are increased in the plasma of patients with depression [135].

## Role of Obesity and Metabolic Parameters

Obesity has been associated with treatment resistance [136,137], and is related to atypical depression [138,139], which consistently also shows lesser therapy response to standard antidepressants [3]. Obesity in depressed subjects is correlated with depression symptoms [18,140,141]. Obesity related metabolic changes are an increase in triglyceride- and LDL levels. The increase in LDL appears to be somewhat specific to patients with atypical depression [142].

Furthermore, CPR and smoking predict increases in lipid levels two years later in a mixed population from the NESDA study, which includes patients with anxiety and depression [143]. This indicates that inflammation leads to metabolic disturbances. Vice versa, altered lipid metabolism can activate the toll like receptor associated NLRP3 pathway: free unsaturated fatty acids, like palmitate, induce inflammation in microvascular endothelial cells [144]. This led to a reduction of ZO-1/ZO-2 adhesion factors. RAAS-activation has a link to vascular inflammatory changes and influences inflammatory parameters in plasma [145,146]. High fat diet is associated with brain inflammation which is mediated via activation of brain RAAS [147]. Obesity induces vascular inflammation and is related to white matter dysfunction. This is prevented by the ATII antagonist canrenoate [148]. These associations show an integral mutual interplay between altered lipid metabolism, inflammation and the renin-angiotensin aldosterone system.

The question arises if manipulation of just one of the systems can be beneficial? Regarding obesity and related lipid alterations, reduction of obesity is related to beneficial clinical outcomes, but with limitations. For example, time restricted eating led to a reduced weight and reduced food addiction score in patients with food addiction, which was accompanied by a significant increase of BDNF and a reduction of lipopolysaccharide binding protein (LBP), a co-factor the TLR4-receptor, in the intervention vs. the control group, but stress levels did not change after 8 weeks of treatment [149]. Bariatric surgery improved depression [150], but may lead to higher levels of suicide [151]. Whereas obesity is associated with brain atrophy [152,153], reduction in weight re-balances sympathovagal activity [154] and improves brain morphology [153,155]. With weight loss aldosterone plasma concentration was reduced in subjects, who had a metabolic syndrome at baseline [128]. This study showed that weight loss was associated with a reduction of CRP, insulin, leptin and it reduced sympathetic activity as expressed by a reduced low frequency HRV. Furthermore, a reduction in salt appetite, as determined by urine sodium content, was observed. The change of inflammatory markers correlated with the change in aldosterone levels. However, a large study found an increase in BMI under treatment was associated with a better therapy response, in particular in patients with a low BMI at baseline [156]. Blood pressure was not reported in this study. It is not clear if the latter finding is related to an increase in appetite, as expected with the improvement of melancholic symptoms, but the association of clinical improvement with weight gain shows that increased weight is not universally associated with higher depression severity. As always, the context of the determined biomarkers is important.

The combination of these characteristics: increased inflammation, obesity and metabolic abnormalities, autonomic dysregulation based on hyperaldosteronism and consequently central MR activation, as well as signs of atypical depression could constitute a specific biological subtype of major importance.

## Clinical Relevance

We described a form of depression, which shows signs of metabolic, inflammatory and neuroendocrine alterations, including a lower level of cortisol and potentially higher level of aldosterone. This form is unfortunately characterized as “atypical”, which is true when compared to the textbook form of depression, which often characterized melancholia. Importantly and often overlooked, this form of depression is prevalent in females and in particular young females, which show atypical features in about 80 % [4,157,158]. In addition, these patients show an earlier age of onset in comparison to non-atypical patients, signs of somatization, an increased risk of drug abuse [159]. This is a crucial group of patients, which do frequently not respond to the first line psychopharmacological treatment option of SSRIs. There is evidence that they respond to compounds, which increase noradrenergic and dopaminergic activity, in particular monoamine oxidase inhibitors [160] and interestingly St. John’s wort [161,162], both of which are related to an increase in dopaminergic activity [120,163]. This is of interest as dopaminergic dysfunction appear to be a primary consequence of inflammation, as observed in depressed patients, who show signs of inflammation: Treatment with l-dopa, i.e., and increase in dopaminergic activity, was beneficial in

these subjects [164]. Complementary to this mechanism, aldosterone has a direct effect on dopaminergic transmission [48,91,165], which may explain the clinical dopamine deficiency syndrome. This may point to a further understanding of this disorder as a monoamine deficit disorder, besides other characteristics.

How these changes are mediated is not entirely clear. A role of the autonomic nervous system is suggested by the observation that autonomic changes are associated with metabolic alterations: lower HRV in patients with depression is associated with metabolic disturbances [166]. Cardiac physiologic markers, including heart rate, low cardiac autonomic balance and low RSA are associated with abnormal metabolic markers [167] and even predicted the development of metabolic abnormalities, including lower HDL [19]. This may point to autonomic dysfunction as the primary disturbance. In this context, the role of vagal activity is of importance and complex: The sensory (afferent) vagus is involved in sensing satiety [168], which may be interrupted in subjects with hyperphagia. Regarding efferent vagal pathways, high levels of central obesity, as expressed by waist circumference, is consistently related to low HRV as a potential sign of low vagal activity [169]. Low HRV and low baroreflex sensitivity are also associated with MRI assessed higher liver fat content patients with early type II diabetes [170]. Accordingly, weight loss leads to an increase in HRV [154]. Vice versa, recent meta analysis of auricular vagus nerve stimulation shows beneficial effects on glucose tolerance and BMI, but the relevance of the effect size was questioned [171]. However, other studies show that vagus nerve blockade in obese subjects [172] or vagotomy in patients with obesity [173] and in mice [174] improve metabolic function. This makes actually intuitive sense, as the vagus nerve is generally regarded as a rest and digest nerve. Metabolic parameters are in fact regulated by the autonomic nervous system in complex ways [175]. An increase in sympathetic activation is associated with lipolysis and an increase in triglycerides [176]. The role of increased vagal activity in health conditions requires further study [177].

Regarding the question which of these systems should be primarily targeted to achieve a clinical benefit a recent study showed that a reduction of lipids and inflammation, may not be sufficient to improve the underlying pathophysiology: reduction of these markers with a statin as an adjunct treatment to standard antidepressants in comparison to placebo in patients with depression did not have any effect on clinical outcome [178]. These findings imply that the root cause of the disorder is upstream of inflammation and lipid dysregulation. One may consider the role of the autonomic nervous system [177].

## Brain Imaging Studies

The characteristics which define a subtype with immune-metabolic changes are an increase in BMI or triglyceride levels and an increase of inflammation markers. In extension this may be associated with a reduced cortisol and increased plasma aldosterone concentration and autonomic dysfunction. Do these markers have consequences for brain morphology? We demonstrated that an increase in BMI and triglycerides are associated with an increase in the volume of the lateral ventricles of the brain [179,180] and that ventricular volumes at baseline were related to treatment outcome. Inflammation has been demonstrated as a potential cause for ventricular volume enlargement, for example in patients with multiple sclerosis [181]. More specifically, the relationship between immune-metabolic forms of depression and increased ventricular volume was confirmed in a large observational study [182]. An increase in ventricular volume was contributed to an increase in the volume and increased activity of the choroid plexus [181]. Moreover, the association between increased choroid plexus volume and inflammatory markers has been confirmed in patients with bipolar disorder [183,184] and major depression [185].

Alterations in gene expression of the choroid plexus have been observed in patients with depression, in particular of markers of transforming growth factor beta (TGFbeta) [186]. As patients with primary hyperaldosteronism have reduced TGFbeta1 plasma levels, which could be reversed with spironolactone [187], a causal link may exist. In our studies an additional feature occurred: We found an association between enlarged ventricles and higher volume of the choroid plexi with a

reduction in anterior and medial parts of the corpus callosum [179,180], confirming earlier observations [188]. How these changes are mediated is not immediately clear. We proposed a model, in which the change of the choroid plexus is a consequence of autonomic dysregulation, which leads to an increase in CSF release and potentially a compression of parts of the corpus callosum [189]. Therefore, balancing the autonomic nervous system may be a priority in order to improve these conditions.

## The Role of Childhood Trauma

Childhood trauma has been associated with neuroendocrine characteristics, in particular hypocortisolism, inflammation and autonomic alterations, with a link to orthostatic dysregulation and baroreceptor dysfunction [190]. Furthermore, high aldosterone levels and low blood pressure occurs in subjects with a history of childhood trauma [191]. Traumatization affects brain morphology: Higher volumes of the brain ventricles and smaller volumes of the corpus callosum in comparison to control subjects were observed in traumatized children, who developed PTSD [192,193]. Accordingly, and in line with our studies, white matter integrity of the corpus callosum as measured by fractional anisotropy (FA) was reduced in bipolar subjects with higher levels of childhood trauma and higher levels of inflammation [194]. This study is based on the same sample which showed larger choroid plexus volumes with inflammation [184]. This observation has parallels to morphological changes in patients with depression less responsive to therapy [179,180]. It further supports the association between a history of childhood trauma and risk of antidepressant treatment refractoriness [195,196].

## Possible Therapeutic Interventions

In order to understand the plausibility of a targeted pharmacological intervention it is useful to understand the physiology of the intervention for a given clinical outcome. The most relevant and broadly studied one in this context is physical exercise as a treatment of depression [197]. There is preliminary evidence that atypical depression is particularly sensitive to exercise [198]. Furthermore, the combination of exercise to sertraline increases parameters of HRV, which is regarded as an increase in vagal tone [199]. In our context, it is of interest to note that exercise does not only reduce weight, but also reduces ATII, aldosterone and norepinephrine levels in the general population [200]. This has not been studied in patients with depression. As already reported, weight loss induced by Bariatric surgery is associated with a reduction in aldosterone concentration [201], normalization of brain morphology [202] and improvement of depressive symptoms. This supports a role of aldosterone in the characterized forms of depression.

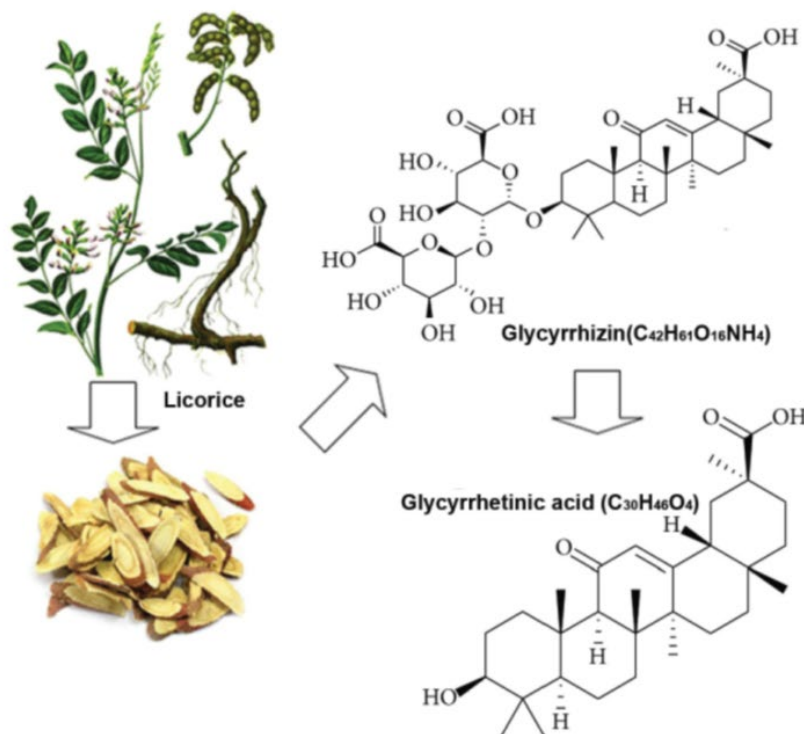
Regarding pharmacological interventions, the MR agonist fludrocortisone showed some beneficial effect in speeding up recovery in patients with depression [45]. Interestingly, fludrocortisone leads to a suppression of aldosterone release via feedback mechanism. Alternatively, ATII antagonists have shown benefits, primarily in open label studies (see [48]). A limitation of this approach is that ATII antagonists not only reduce aldosterone levels, but also blood pressure, which may counteract its efficacy, as both signals work in opposition at the NTS.

## Glycyrrhizin/Enoxolone

### *Glycyrrhizin Reduces Aldosterone via Inhibition of the 11betaHSD2*

An alternative approach to reduce aldosterone plasma concentrations and at the same time increase blood pressure was identified [203]: Glycyrrhizin, from the licorice plant, *glycyrrhiza glabra*, and its active metabolite glycyrrhetic acid (enoxolone) acts as an inhibitor of the 11betaHSD2.

Figure 1:

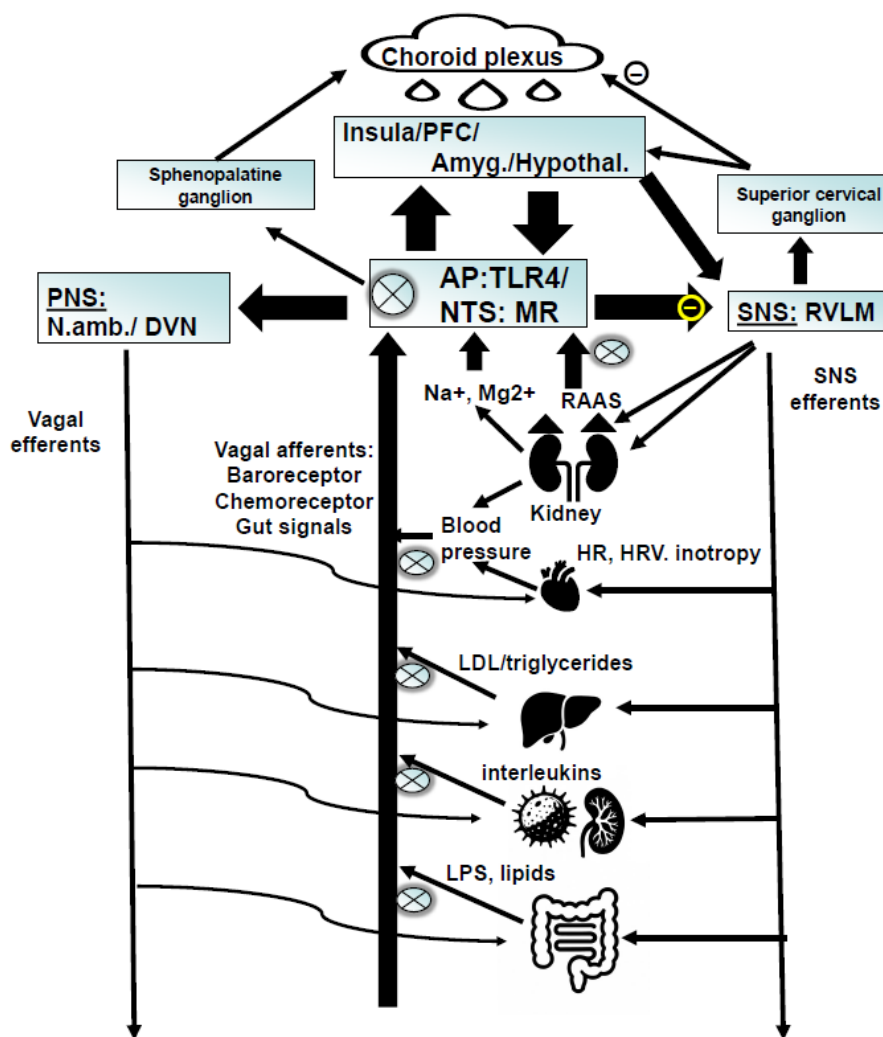


**Figure 1. Source of glycyrrhizin and enoxolone:** Glycyrrhizin is derived from *glycyrrhiza glabra*. Glycyrrhetic acid (Enoxolone) is the active metabolite of glycyrrhizin. It is generated in the gut by hydrolysis by gut bacteria (from [255]).

This inhibition mediates a reduction of aldosterone release (see below for details). These compounds are also antagonists at the TLR4. Glycyrrhizin and enoxolone have been widely studied for their pharmacological and biological properties [204]. Their pharmacokinetic and toxicological profile are well known. As glycyrrhizin is converted into enoxolone in the gut and only enoxolone is taken up to act systemically, we regard these compounds as equivalent and don't differentiate their actions in the following [205]. A related compound is a modified enoxolone, carbenoxolone, which is discussed in the same way.

Enoxolone acts on 11 $\beta$ HSD2. This is the same enzyme, which protects MR in the NTS and the kidney from being occupied by cortisol/corticosterone, by its intracellular metabolism into the inactive cortisone, therefore, allowing aldosterone to compete. The dose range is critical for its effect: enoxolone acts in a reversible fashion in a dose of 500 mg daily, but may be irreversible in a dose of 1500 mg daily [206]. The main target based side effects can be summarized under pseudohyperaldosteronism, i.e., an increase in blood pressure and hypokalemia [204] based on the stimulation of MR by cortisol. On the basis of these parameters a non effect dose of approx. 100 mg daily has been described [207,208]. As a consequence of the MR stimulatory effect of glycyrrhizin/enoxolone, a feedback mechanism acts to reduce aldosterone release [209–212]. Due to the MR stimulation an increase in blood pressure can be observed despite the reduction in aldosterone levels. Recently, in a crossover study in healthy subjects a dose as low as 100 mg glycyrrhizin demonstrated to reduce renin and aldosterone and to slightly increase blood pressure [213]. The blood pressure increasing effect of 11 $\beta$ HSD2 inhibition is in part due to a direct action at vascular MR leading to a vascular contraction. This involves an increased sensitivity to norepinephrine and cortisol [214], as shown in healthy subjects. The vascular effect of glycyrrhizin from licorice (dose 290 -370 mg for two weeks) is reflected by an increase in aortic and popliteal pulse wave velocity, alongside the increased blood pressure and a reduced orthostatic response [215]. In addition, this study showed a reduction in low frequency heart rate variability, potentially as a sign of reduced sympathetic activity.

Figure 2:



**Figure 2. Schematic characterization proposed to summarize the underlying neurobiology with targets for enoxolone:** 1. Enoxolone inhibits the release of aldosterone from the adrenal cortex due to the fact that it inhibits the kidney and endothelial 11 $\beta$ HSD2. This allows cortisol to bind to peripheral MR, which via feedback inhibits renin release, the generation of angiotensin and finally the activation of ATII mediated aldosterone release. The reduction of aldosterone reverses the inhibition of NTS neurons, normalizes baroreceptor reflex and other inputs from the afferent vagus. As a consequence, efferent vagus activity is increased, which has effects on several levels: improvement of cardiovascular regulation; sensitization of the neuro-inflammatory reflex; improvement of metabolic activity. 2. Enoxolone also inhibits TLR4 activity with direct consequences at immune cells; sensitization of the neuro-immune reflex via vagal (nodose ganglion); reduced inflammation of the gut. PFC: prefrontal cortex; Amyg: amygdala; hypothal.: hypothalamus; NTS: nucleus of the solitary tract; AP: area postrema; PNS: parasympathetic nervous system; SNS: sympathetic nervous system; N.amb.: nucleus ambiguus; DRN: dorsal vagal nucleus; RVLM: rostroventrolateral medulla; HR: heart rate; HRV: heart rate variability; RAAS: renin-angiotensin-aldosterone system; LDL: low density lipoprotein. MR: mineralocorticoid receptor; TLR4: toll like receptor 4; LPS: lipopolysaccharide (endotoxin). X : target for enoxolone.

A direct CNS effect may not be relevant for the action of glycyrrhizin/enoxolone in the proposed dose range, but should be briefly reviewed here for completeness: The administration of glycyrrhizin intracerebroventricularly in rats leads to an activation of the hypothalamic paraventricular nucleus, which goes along with an increase in blood pressure and renal sympathetic activity [80] by direct sensitization of the PVN neurons to cortisol/corticosterone. In this context it is important to keep in mind that our attempt is to reduce aldosterone peripherally, therefore, we expect a reduced central

MR activation in the projected dose range as a consequence. This targeted approach can be reached as enoxolone crosses the blood brain barrier only to a limited extent [216]. It is of interest to note that there is a potential alternative mechanism for enoxolone and the related compound carbenoxolone to affect hypothalamic activity: carbenoxolone administration into the ventromedial hypothalamus reduced hypothalamic theta oscillations in a sodium-channel dependent way. Mediation by gap junction block was suggested [217]. Involvement of gap junction blockade was also proposed for the effect of carbenoxolone to block vagally mediated hippocampal theta oscillations [218]. However, these effects are unlikely to be relevant in the proposed doses due to the limited BBB permeability.

#### *Glycyrrhizin Reduces Inflammation via TLR4 Inhibition*

Glycyrrhizin/enoxolone have been recognized as neuroprotective by inhibiting inflammation via TLR4 antagonism and reduction of high mobility group box-1 (HMGB-1) protein [116,117,219] and action at its receptor RAGE [220,221], for an overview see [102] [111,222,223].

Glycyrrhizin reduces the generation of oxidative stress from neutrophils [224]. In addition and complementary to this effect, enoxolone protects against oxidative stress in intestinal epithelial cells by activating the PI3k/Akt pathway [225]. Similarly, advanced glycation endproducts (AGEs) induced oxidative stress and inflammation in umbilical cord epithelial cells, which was inhibited by glycyrrhizin [226]. In a hamster model, an extract from glycyrrhiza glabra had anti-inflammatory effects against SARS/Cov-2 infection, which reflects direct inhibitory action at neutrophils and reduced oxidative stress [227]. A suppression of the differentiation of Th1, Th2 and Th17 cells was involved in the action of glycyrrhizin in this study. A direct effect of glycyrrhizin in T-cells was confirmed in another experiment [228]. Overall, it appears that one target of glycyrrhizin/enoxolone is immune cells.

An indirect immune suppression can be implied by the action of these compounds in the function of the NTS. The neuroimmune reflex [118,119] establishes a feedback mechanism to suppress increased peripheral inflammation. The key anatomical structures are the vagus afferents, connecting to the vagus nerve and the efferent vagus from the nucleus ambiguus and dorsal vagal nucleus. These efferents to the spleen suppress immune response, as determined by interleukin release, via cholinergic alpha-7 nicotinic receptors.

This association between the central element of the anti-inflammatory reflex and its association with the area postrema leads to an additional important anatomical location relevant for the anti-inflammatory effect of enoxolone: TLR4 is expressed in astrocytes of the area postrema and NTS, the latter being the main target for aldosterone! This demonstrates an intriguing synergism between the main effects of enoxolone to affect NTS activity on the one hand by targeting astrocytes via TLR4 and neurons via 11betaHSD2.

#### *Behavioral Effects of Glycyrrhizin/Enoxolone*

An animal model (single prolonged stress) leads to an induction TLR4 and HMGB1 expression in the basolateral amygdala, which was accompanied by neuroinflammation. These changes could be inhibited by glycyrrhizin [111,112] Glycyrrhizin blocks the effect of subchronic restraint stress: this form of stress induction inhibits locomotor activity, which can be reversed by glycyrrhizin [229]. The behavioral effect was accompanied by an increase in corticosterone release. Interestingly, the beneficial behavioral effect was observable for rats treated for 10 days, but not for several weeks. In another study glycyrrhizin, as active component of an extract, reduced salt appetite and increased HPA axis activity, when administered orally in a dose of 150 mg/kg per day for two weeks. The extract had a concentration of glycyrrhizin of approx. 7% [230]. The reduced salt appetite is a sign of reduced central MR activation, as intended. This was accompanied by an anxiolytic effect and, again, an increase in corticosterone release. The increase in aldosterone was restricted to unstressed, not stressed rats [231]. A non-significant reduction in aldosterone was observed, which overall points to a reduction in the aldosterone/corticosterone ratio.

Glycyrrhizin counteracts depression like behavior in mice administered with LPS, the ligand of the TLR4-receptor [232]. Zhang et al. (2014) and Kamisili [233] pointed to the importance of the inhibition of the NFkB-IL-17-pathway in the action of glycyrrhizin for brain protection. This is relevant, as brain morphological changes, mediated by inflammatory processes, may be mediated by this inflammatory pathway. Action at the choroid plexus structures appear to be involved and may mediate depression [183]. The choroid plexus appears to be an entry point of IL-17 producing Th-17 T-helper cells, which play a key role in demyelination [234]. We are currently researching if enoxolone leads to changes in brain morphology in patients with depression and for which patients this may be related to treatment outcome (<https://www.clinicaltrials.gov/study/NCT05570110>).

In addition, the same inflammatory pathway is also relevant for the beneficial behavioral effect of glycyrrhizin via improved integrity of the gut [235,236]. In line with this with these observations, a glycyrrhizin containing extract downregulated the expression of angiotensin converting enzyme 2 (ACE2)[231], potentially due to the reduced inflammatory stress [237].

The expected reduction of aldosterone induced by this compound may also induce an anti-inflammatory effect. Glycyrrhizin demonstrated anti-inflammatory properties in an ischemia model via inhibition of TLR4 receptors, which was similar to effects observed with the ATII antagonist candesartan [238]. This point back to the synergism of aldosterone and inflammatory activity via aldosterone's action to boost TLR4 activity [129].

#### *Effect of Glycyrrhizin/Enoxolone on Metabolic Parameters*

Glycyrrhizin demonstrated an effect on metabolic parameters: in an animal model (doxorubine induced cardiomyopathy) triglyceride levels decrease, whereas HDL levels increase [239], in addition to an increase in blood pressure. Four week treatment with an ethanolic extract of licorice led to a similar reduction in triglycerides, plasma glucose and weight gain in high fat diet (for 10 weeks) induced metabolic disturbance in rats. This was accompanied by changes in gut flora, liver steatosis and signs of reduced liver inflammation [240]. Oral administration of glycyrrhetic acid (enoxolone) leads to an improved lipid profile and a reduced weight gain in a high fat diet model [241]. The effect on lipid metabolism and inflammation may involve the stabilization of ACE2 in the liver [242] in an LPS/D-galactosaminase model. It may also involve a change in sympathetic hepatic nerve activity, which may potentially be mediated via the gap-junction inhibitory effect of these compounds, as described for carbenoxolone [243]. Finally, metabolic changes in obesity involve higher levels of free unsaturated fatty acids, which induce inflammation and a reduction of ZO-1/ZO-1 adhesion factors in microvascular endothelial cells. These changes could be reversed with the administration of glycyrrhizin [144].

#### *Glycyrrhizin Reverses Catecholamine Depletion – Autonomic Activity as Primary Driver?*

Back to the starting point focusing on catecholamines and autonomic regulation: Schildkraut's framework of the catecholamine deficiency hypothesis of depression may best apply to patients with fatigue and/or low blood pressure! The overlap between these symptoms is well documented [199,244]. Ammonium glycyrrhizinate (100 and 150 mg/kg) intraperitoneally, i.p.) has demonstrated a reversal of behavioral changes induced by reserpine [245], potentially mediated by an inhibition of monoamine oxidase. In line with this observation, an antidepressant effect of glycyrrhizin could be inhibited by antagonism at noradrenergic and dopaminergic receptors: reduced immobility was observed in the forced swim at a dose of 150 mg/kg extract containing approx. 7% glycyrrhizin. 75 mg/kg or 300 mg/kg were not effective, supporting an optimal dose range. The effect could be blocked by sulpiride (D2 antagonist) or prazosin (alpha1 antagonist) [246]. In a further experiment, utilizing a norepinephrine depletion model with fusaric acid, a dose dependent reversal of anxiety related behavior was observed with the administration of glycyrrhizin, which was also accompanied by an increase in brain metabolic signs (increase in ATP) and integrity (increase in brain derived neurotrophic factor, BDNF) [247]. Doses of 200 mg/kg and 300 mg/kg orally (dissolved in distilled water), but not 100 mg/kg were effective on these parameters.

## Clinical Studies:

How do the reported biological activities of glycyrrhizin translate into clinical outcome? Beneficial effects in animal models of depression and anxiety were reported above. The number of clinical observations is, however, limited. Glycyrrhizin is a common ingredient in Japanese, Chinese and Ayurvedic medicine, for example of the Japanese Yokukansan and showed beneficial effects on depressive symptoms in a placebo-controlled trial [248,249]. It is, however, difficult to attribute this to any specific ingredient. In clinical studies in patients with depression glycyrrhizin in a defined concentration as component of an extract from glycyrrhiza glabra demonstrated antidepressant activity in comparison to a historic control [203]. The effect was most pronounced in a patient group with a low vs. higher systolic blood pressure (median split at 127 mmHg). Clinical improvement in the glycyrrhizin treated subjects was associated with a reduced heart rate and a shortening of sleep duration. The anti-inflammatory effect of glycyrrhizin is another important element of its efficacy: In a randomized placebo controlled trial with adjunct treatment of glycyrrhizin to an SSRI an overall statistically significant benefit of glycyrrhizin vs. placebo was observed, but that effect was mainly restricted to subjects with a higher level of C-reactive protein as a sign of systemic inflammation [250]. Subjects were primarily male (89%) and had on average a normal BMI of approx. 23.4, i.e., did not show metabolic abnormalities. Besides a significant clinical improvement, the actively treated subjects showed a reduction in TNFalpha and IL1beta, which was significantly different from the placebo group. An interim analysis from an ongoing randomized placebo-controlled study with pure enoxolone, 100 mg vs. placebo, in hospitalized patients with depression [251] confirmed target engagement by a significant reduction of the plasma aldosterone/cortisol ratio and of plasma CRP. Treatment responders showed preferentially higher CRP levels at baseline as well as a history of more childhood abuse. Put together, we provided evidence for an antidepressant effect of glycyrrhizin/enoxolone in combination with standard antidepressants in a population, which can be identified on the basis of biological (inflammation, autonomic disturbances, high aldosterone/cortisol levels) and anamnestic (childhood trauma) parameters. We hypothesize that the assessments of these biomarkers can be done BEFORE any standard antidepressant is applied, which may avoid the clinical expression of treatment refractoriness. However, these subjects can be regarded as treatment refractory based on their underlying biology. Therefore, enoxolone/glycyrrhizin could be a first line treatment for subjects with high risk of treatment resistance.

## Limitation

The current summary of the effects of glycyrrhizin/enoxolone focus on the overlap with a specific form of depression, which is less responsive to standard antidepressants and which show signs of inflammation, increased aldosterone levels, low cortisol and low blood pressure. The motivation to study these compounds was to find an intervention which reverse these biomarker changes and the underlying neurobiology, therefore improving clinical outcome. We therefore reported aspects of enoxolone, which are supportive of this concept, and are the main characteristics of this compound. Other properties have not been discussed in detail. These include the antiviral effect of these compounds [252], anticancer, liver protective, SARS-Cov2 targeting and also 11betaHSD1 inhibiting properties [253] other properties, for an overview see [204] [254].

## Conclusion

We identified biomarkers related to treatment resistance to standard antidepressants in depression. These include autonomic (low blood pressure, low heart rate variability), inflammation (higher CRP), metabolic (higher triglycerides and higher BMI) and neuroendocrine (high aldosterone/cortisol ratio) markers. The underlying neurobiology points to a dysfunction of peripheral MR activity, which leads to pontine autonomic dysregulation. Glycyrrhizin/enoxolone has specific properties to overcome the underlying neurobiology. The clinical effect in a specific subgroup is supported by preliminary data. Additional studies are ongoing to further test these findings.

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