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Control of ACTH Secretion by Excitatory Amino Acids

Functional Significance and Clinical Implications

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The involvement of excitatory amino acids in the control of ACTH release is well established. Activation of ionotropic glutamate receptors has a stimulatory effect on ACTH release, while the role of metabotropic receptors is not yet understood in detail. Glutamatergic regulation of ACTH release has a clear significance for the stress response and neuroendocrine functions during development. A dysregulation of the hypothalamic–pituitary–adrenocortical (HPA) axis has been reported in several psychiatric and neurological disorders. So far, only fractional indices on the clinical importance of the interaction between glutamate and ACTH secretion have been obtained in both preclinical and clinical studies. Some antidepressant drugs, such as tianeptine, which were found to modulate ACTH release, appear to interfere with brain glutamatergic system. Changes in ACTH and cortisol release may be of importance for mood stabilizing effects of antiepileptic drugs modulating glutamate release, such as lamotrigine. Brain glutamate and HPA axis interaction seems to be of importance in alcohol and drug abuse. Little information is available on ACTH release in response to glutamate-modulating drugs used in the treatment of schizophrenia and Alzheimer disease. Nevertheless, pharmacological interventions influencing interaction between glutamate and the HPA axis are promising treatment possibilities in psychiatry and neurology.

Key Words: ACTH; cortisol; glutamate; stress; depression; drug abuse.

Introduction

There is no doubt that excitatory amino acids (EAA) are involved in the multifactorial control of ACTH release. Stimulation of several heterogeneous subtypes of glutamate receptors leads to activation of the hypothalamic–pituitary–adrenocortical (HPA) axis. The involvement of EAA neurotransmission in neuroendocrine regulation is just a part of its function in the brain. For example, glutamate plays an important role in the processes of learning and memory and in neural plasticity in general. Disturbances in glutamate transmission belong to pathogenic factors assumed to be involved in several brain diseases, such as epilepsy, neurodegenerative diseases, depression, schizophrenia and drug dependence. These disorders are often associated with chronic enhancement of glucocorticoid release and dysregulation of the HPA axis. Thus, there is a great potential that modulation of glutamate-induced changes in ACTH and glucocorticoid release under pathological conditions would be of clinical significance.

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Control of ACTH Secretion by EAA Under Basal Conditions

Excitation of the HPA axis by central administration of glutamate was demonstrated 30 yr ago *(1)*. Much later, the development of pharmacological agents allowed detailed studies on the role of glutamate receptors in the control of ACTH release considering different receptor subtypes. Glutamate receptors are divided into ionotropic and metabotropic types of receptors, both of them having several receptor subtypes. Extensive knowledge is available particularly on the *N*-methyl-D-asparte (NMDA) ionotropic receptor subtype. Following anecdotal observation of increased cortisol release by high doses of a racemic form of NMDA (NMA) in studies evaluating gonadal function *(2)*, evidence on the stimulatory role of NMDA receptors on ACTH release in rats was provided independently in two laboratories *(3,4)*. Peripheral administration of NMA or NMDA induced a dose-related increase in ACTH secretion, which was possible to prevent by pretreatment with NMDA receptor antagonists *(3,4)*. ACTH release was found to be enhanced already by low doses of NMDA, which failed to modify the secretion of prolactin or catecholamines *(4)*. Agonists of other ionotropic glutamate receptor subtypes, such as kainate were found to stimulate ACTH or corticosterone release *(5)*.

Interestingly, the activation of the HPA axis is induced not only by glutamate agonists, but also by acute treatment with ionotropic glutamate receptor antagonists. In rats, enhanced ACTH and/or corticosterone release was observed following acute administration of non-competitive NMDA

antagonists with high (dizocilpine) *(6,7)* or low affinity (dextromethorphan) *(8)* as well as by non-NMDA receptor antagonists (DNQX) *(9)*. We have speculated that it might be a consequence of a non-specific activation of the HPA axis in response to a novel psychological state induced by psychotropic drugs *(7)*. Indeed, stimulatory effects of dizocilpine on hormone release disappear within 3–4 d of repeated injections *(6,10)*. In primates, repeated self-administration of the low-affinity NMDA antagonist ketamine inhibited HPA axis activity *(11)*.

Current information on the action of metabotropic glutamate receptor agonists and antagonists is less consistent. The metabotropic glutamate (mGlu) receptor agonist 1-aminocyclopentane-1,3-dicarboxylic acid (ACPD) has been shown to increase plasma corticosterone levels in rats *(12)*. Metabotropic glutamate receptors acting via multiple second messenger pathways are divided into three main groups. Central administration of group I and group III mGlu receptor agonists induced an elevation of serum corticosterone *(13)*. Agonists of group II mGlu failed to induce significant changes in corticosterone levels *(13,14)*. Similarly as in the case of ionotropic glutamate receptor modulating drugs, some of mGlu antagonists given alone also increased corticosterone secretion, e.g., MPEP [2-methyl-6-(phenyl-ethynyl)-pyridine], a group I mGlu antagonist in some *(13,15)* but not all *(14)* studies. The mGlu antagonist LY341495 injected intraperitoneally in doses known to be group II selective failed to elevate corticosterone levels in rats *(13)*, but did so in mice *(14)*. Intracerebroventricular administration of higher doses of LY341495, which may influence group I mGlu receptors, increased corticosterone release *(13)*. Actually, the two groups of authors mentioned *(13,14)* came to different conclusions as to the relative importance of individual subtypes of mGlu receptors in the control of the HPA axis. Scaccianoce et al. *(14)* support their assumption on an important role of group II (mGlu2/3) receptors by observed changes in CRH release from isolated hypothalami following their pharmacological modulation.

The action of glutamate receptor agonists and antagonists on the HPA axis is supposed to be centrally mediated. Corticotropin-releasing-hormone (CRH) neurons of the hypothalamic paraventricular nucleus (PVN) do express both ionotropic *(16,17)* and metabotropic *(18)* glutamate receptors. Moreover, the majority of CRH neurons in the PVN express mRNA coding for type-2 vesicular glutamate transporter, a marker of glutamatergic neuronal phenotype *(19, 20)*. In vitro studies have demonstrated that EAA are able to stimulate CRH secretion via both ionotropic and metabotropic glutamate receptors *(14,21)*. In a recent study using lesions of the PVN, Zelena et al. *(22)* have demonstrated that NMDA and kainate may activate the HPA axis at central (PVN) level and that vasopressin has a minor role in glutamate–HPA axis interaction.

It may be argued that some of the glutamate agonists exerting an action on ACTH release (e.g., NMDA) do not readily cross the blood–brain barrier to reach the regulatory sites in the hypothalamus after peripheral administration. One possible explanation is the mediation of their action via brain regions lacking blood–brain barrier function, such as the subfornical organ or the area postrema *(23)*. The effects of glutamatergic drugs at the pituitary level are not likely, while an action at the adrenal gland cannot be excluded regarding the presence of several types of glutamate receptors *(24)*.

Functional Significance of the Control of ACTH Secretion by EAA: Stress Response

One of the most prominent functions of the HPA axis is its involvement in the stress response. Thus, a principal question in evaluating the functional significance of the control of ACTH secretion by EAA is the possible relationship of the HPA axis and EAA under stress conditions. An essential prerequisite for such a relationship is that brain glutamatergic system would change in response to stressful events. This seems to be the case as proved by different methodological approaches. Using microdialysis techniques, a rise in extracellular levels of glutamate in several brain regions were observed during stress paradigms *(25,26)*. In this, as well as other laboratories, changes in selected glutamate receptor subunit gene expression in stress-related brain regions have been demonstrated following acute and repeated stress exposure *(27–29)*. Mentioned changes in appropriate mRNA levels were observed several hours after initiation of stress, while others failed to find any alterations immediately after the stress exposure *(30)*. Stress-induced increases in the expression of some glutamate transporters have recently been reported *(31)*.

The physiological importance of endogenous EAA in the control of stress-induced ACTH release has been approached using glutamate receptor antagonists. Peripheral injection of a competitive NMDA receptor blocker, which does not cross the blood–brain barrier, failed to modify ACTH response during stress. However, pretreatment with the centrally acting NMDA antagonist dizocilpine (MK-801), although increasing basal ACTH concentrations, attenuated ACTH response during immobilization stress, as shown by Jezova et al. *(7)*. Similar effects were observed using intracerebroventricular administration of the AMPA/kainate receptor antagonist DNQX *(8)*. Thus, glutamate effects via both NMDA and non-NMDA ionotropic glutamate receptors seem to be involved in stress-induced ACTH release. Interestingly, glutamatergic mechanisms also participate in the control of another important stress attribute, namely, the sympathoadrenal system and stress-induced catecholamine release *(7)*.

According to our further studies, the contribution of glutamatergic neurotransmission to the neuroendocrine response during stress appears to vary with regard to the stress stimulus applied and the stress hormone studied *(10)*. Re-

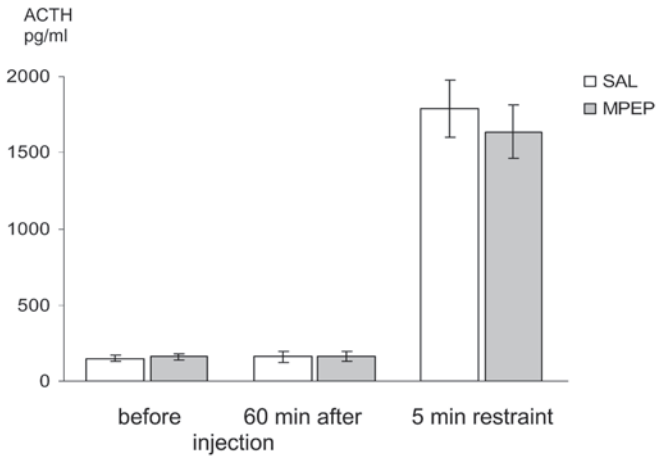

Fig. 1. Lack of effect of group I metabotropic glutamate receptor antagonist MPEP (1 mg/kg ip) on ACTH levels under basal conditions and during short restraint stress in cannulated rats. SAL, isotonic saline. Data are expressed as means ± SEM.

peated treatment with the NMDA antagonist dizocilpine, the selective AMPA antagonist GYKI52466, or their combination failed to modify the rise in plasma ACTH levels elicited by footshock or ether inhalation. The combined treatment with dizocilpine and GYKI52466 resulted in an inhibition of ACTH release during immobilization stress. The magnitude of this inhibition was comparable to that induced by separate blockade of glutamate receptor subtypes. A different pattern was observed in the changes of stress-induced prolactin release *(10)*.

With respect to metabotropic glutamate receptor antagonists and their effects on stress-induced ACTH release, no data are currently available. Corticosterone response to a despair stress (forced cold-water immersion) was not modified by pretreatment with an antagonist (LY341495) or an agonist (LY379268) of group II mGlu receptors *(14)*. Pretreatment with MPEP, a group I mGlu antagonist, had no effect on corticosterone response to a 15 min restraint *(15)*. Our preliminary data indicate a lack of MPEP action on stress-induced ACTH secretion (Fig. 1).

Functional Significance of the Control of ACTH Secretion by EAA: Developmental Aspects

General importance of glutamate neurotransmission for various developmental processes is well known. On the other hand, the developing brain is particularly vulnerable to neurotoxic effects of glutamate including significant modulation of anterior pituitary hormone secretion *(32)*. A contributing factor to possible exaggerated effects of exogenous glutamate on neuroendocrine brain regions is an altered function of the blood–brain barrier during early stages of life *(33)*.

A long time ago, Olney *(34)* showed that peripheral administration of monosodium glutamate (MSG) to neonate rodents induced a long-lasting neurotoxicity resulting in a so-called "MSG syndrome." The syndrome is associated with several endocrine alterations and obesity. As for the HPA axis, several inconsistent and even contradictory data were published *(23)*. In a detailed study in this laboratory, treatment of neonatal rats with MSG resulted in enhanced proopiomelantocortine (POMC) gene expression per corticotrope of the atrophic pituitary resulting in maintenance of normal pituitary ACTH stores and plasma ACTH levels. Furthermore, we observed a decreased clearance rate of corticosterone, which may explain elevated basal corticosterone levels and prolonged corticosterone responses to stimulation in rats treated neonatally with MSG *(35)*.

It is probable that a bilateral interaction occurs between glutamate neurotransmission and HPA-axis hormones during the development. The lack of maternal corticosterone induced by adrenalectomy produced an increase in brain glutamate of the offspring at 2 wk of postnatal life *(36)*. On the other hand, glutamate agonists activate the HPA axis already in premature animals. In rats aged 3–14 d, the stress-induced ACTH and corticosterone release is lower than that in adults. This time period is called the "stress hyporesponsive period." Agonists of ionotropic glutamate receptors were found to be capable of inducing elevations of ACTH and corticosterone *(37–39)*. This effect appears to be centrally mediated, as the stimulating effect of NMDA and kainate on ACTH release was blocked by passive immunization with a CRH antiserum *(37)*. Moreover, treatment of neonatal rats with glutamate evoked a rise in POMC mRNA levels in the anterior pituitary *(39)*.

In our recent study, prenatal exposure of rats to phenytoin, an antiepileptic drug modulating glutamatergic transmission, resulted in slightly enhanced ACTH response during stress in adult animals, an effect similar to the outcome of prenatal stress exposure *(40,41)*. Some negative consequences of prenatal exposure to maternal stress were reduced by keeping the animals in an enriched environment *(42)*, a condition known to be related to increased neuroplasticity and thus indirectly also to glutamatergic system function.

Clinical Implications of the Control of ACTH Secretion by EAA

Depression and Antidepressant Drugs

The etiology of depression is far from being understood. Next to central monoaminergic transmission, additional neurotransmitter systems, including glutamatergic transmission, appear to contribute to the pathophysiology of affective disorders *(43)*. Likewise, an important role in the development and course of depression is attributed to hormones of the HPA axis. Impaired function of the HPA axis has repeatedly been noted in patients with major depression. Disturbances in feedback mechanisms, increased cortisol release, and, in particular, the hyperactivity of hypothalamic CRH are supported by many clinical findings *(44)*. Moreover, CRH antagonists exert antidepressant and anxiolytic effects

(45). Possible interaction of brain glutamate system and the HPA axis is suggested by some preclinical studies. Changes in glutamate receptor subunit gene expression in brain regions of the reward system together with enhanced CRH gene expression in the PVN were found in an animal model of depressive symptomatology, namely, in spontaneous anhedonia described by Duncko et al. *(46)*.

Modulation of the stress hormones and particularly of the HPA function is thought to be one of the targets of antidepressant therapy. Indeed, decreased levels of plasma cortisol were observed after chronic treatment with several antidepressants. In major depression, a normalization of HPA system abnormalities may be a strong predictor of the clinical course *(47)*. The mechanisms responsible for antidepressant drug effects on ACTH and glucocorticoid secretion may involve glutamatergic pathway. There is accumulating evidence supporting the impact of antidepressant agents on plasticity processes in the hippocampus *(48)* and neuroplasticity is strongly influenced by both glutamate and glucocorticoids. In this respect, the most thoroughly studied antidepressant drug is tianeptine *(49)*. In animal studies, repeated tianeptine treatment was reported to reduce the stress-induced increase in plasma ACTH and corticosterone levels *(50)* as well as reversed negative effects of chronic stress on brain plasticity *(49)*. For example, increase in a glutamate transporter gene expression induced by chronic mild stress (an animal model of depression) was inhibited by tianeptine *(31)*.

In our studies in humans, however, repeated tianeptine treatment stimulated rather than inhibited ACTH release during stress *(51)*. Such observations remind one of the necessity of strong caution in interpreting the animal data in terms of human pathophysiology. Similar activation of stress-induced ACTH release has been achieved by another antidepressant drug citalopram. Citalopram and tianeptine have an opposite effect on brain serotonin reuptake and the mentioned data provide a new insight into the mechanism of action of antidepressant drugs *(51)*. Whether the action of antidepressants on ACTH release during stress is mediated via brain glutamatergic system and related neuroplasticity remains open for further studies.

Bipolar Disorder and Mood Stabilizers

Recent studies suggest that impairments of neural plasticity and glutamatergic system underlie the pathophysiology of bipolar disorder and agents affecting glutamate receptors or release are considered as potential antimanic or mood stabilizing drugs *(52)*. Little information is available on the relationship of these effects to possible interference with ACTH release. Riluzole, a glutamate-modulating agent, has been shown to have antidepressant efficacy in subjects with bipolar disorder *(53)*. This drug failed to modify basal ACTH and cortisol levels or hormonal responses during mental stress in elderly subjects. ACTH levels in response to a physical stressor only tended to be lower after riluzole pretreatment *(54)*.

However, treatment with lamotrigine, a drug used to treat bipolar disorder and among other mechanisms to inhibit glutamate release, exerted clear effects on stress hormone release in young volunteers *(55)*. Lamotrigine significantly inhibited cortisol increase during psychosocial stress based on public speech. These data described by Makatsori et al. *(55)* may be considered as indirect evidence for the involvement of glutamate in the control of the HPA axis in humans. Effects of lamotrigine on stress hormone release may be of value for its mood stabilizing effects. In a recent preclinical study in mice, felbamate, another antiepileptic drug modulating glutamatergic neurotransmission, affected corticosterone release in response to social stress together with signs of antidepressant properties *(56)*.

Drug Abuse and Dependence

Glutamatergic transmission belongs to mechanisms playing important roles in processes underlying the development and maintenance of addiction *(57)*. Many drugs of abuse activate ACTH secretion, and stress is often mentioned as a factor implied in the development of drug and alcohol abuse. Hormones of the HPA axis have also been related to the process of sensitization to intermittent treatment of drugs of abuse *(58,59)*, which is known to include glutamatergic mechanisms *(60)*. Ketamine, a non-competitive NMDA receptor antagonist and dissociative anesthetic agent, blocked the stimulation of ACTH by cocaine and reversed the behavioral sensitization, suggesting that stimulation of EAA receptor function belongs to mechanisms whereby cocaine exerts its effects on neuroendocrine and behavioral activating systems *(61)*. There are several examples of concomitant modulation of ACTH release and glutamatergic system during addictive behavior. Both HPA-axis hormone levels and glutamate receptor subunit gene expression were affected by compulsive voluntary wheel running in Lewis rats prone to addictive behavior *(62,63)*. Morphine treatment, well known to activate the HPA axis in rodents, modulates glial glutamate transporter *(64)* and glutamate receptor gene expression in the brain and in the adrenals *(65–67)*.

Although several aspects of glutamate receptor function are the targets of the development of new therapeutic agents *(68)*, there are only a few treatments of addiction based on modulation of glutamatergic transmission in current clinical practice. Acamprosate, a drug with a complex mechanism of action involving modulation of glutamatergic system, is used in the treatment of alcohol dependence *(69)*. Very limited information is available on the effects of acamprosate on hormones of the HPA axis. Influence of acamprosate treatment on cortisol response to combined dexamethasone/CRH test was evaluated in detoxified alcoholics within the first 3 wk of abstinence *(70)*. The authors reported that 1-wk treatment with acamprosate did not attenuate the

Table 1
Clinically Used Drugs Modulating Glutamate Release and ACTH Secretion

Drug	Clinical use	Information available on ACTH and cortisol
Tianeptine	Antidepressant	↓ stress-induced ACTH levels in animals ↑ stress-induced ACTH levels in humans
Lamotrigine	Antiepiletic drug, mood stabilizer	↓ stress-induced cortisol levels in humans
Ketamine	Anesthetics	↑ basal levels of cortisol in humans and primates
Acamprosate	Treatment of alcohol dependence (anti-craving drug)	No effect on cortisol response to combined dexamethasone/CRH test in humans
Memantine	Treatment of Alzheimer disease	↑ basal levels of ACTH in animals No effect on cortisol in humans

HPA dysregulation observed during early abstinence. Apparently, further studies are needed to understand the role of HPA-axis hormones in the drug addiction including anti-craving treatments. In a pilot study in cocaine-dependent individuals, administration of cortisol increased the craving and so induced a state that is associated with drug abuse *(71)*.

Schizophrenia and Antipsychotic Drugs

The fundamental neurotransmitter involved in schizophrenia is dopamine. However, recent advances have also linked the pathophysiology of schizophrenia with abnormalities of the EAA neurotransmitter system *(72)*. Modulatory effects on ionotropic glutamate receptors may belong to sites of action of some atypical antipsychotic drugs, such as clozapine *(73)*. Patients with schizophrenia may have increased levels of plasma cortisol, and atypical antipsychotic drugs appear to decrease cortisol concentrations *(74)*, although the data are not consistent. Dysfunction of the HPA axis has been linked to some neurodevelopmental damage in the hippocampus, which could involve mainly glutamatergic pathways *(75)*. Nevertheless, no data on possible interaction between ACTH or cortisol release and glutamatergic control in schizophrenia are currently available.

Alzheimer Disease and Memantine

A growing body of evidence suggests that perturbations in glutamatergic systems underlie the pathogenic mechanisms of neurodegenerative disorders *(76)*. Therapeutic interventions with high-affinity glutamate receptor antagonists failed in the treatment of senile dementia, such as Alzheimer disease, because of serious adverse effects. The only glutamate-modulating drug in current clinical use is memantine, a low–moderate affinity voltage-dependent NMDA receptor antagonist *(77)*.

In Alzheimer disease, increased basal activity of the HPA axis and altered stress response have repeatedly been reported *(78)*. Single injection of a relatively high dose of memantine in rats increased ACTH and corticosterone levels as well as gene expression of the CRH in the hypothalamus. A lower dose of memantine potentiated corticosterone elevation in response to cocaine *(79)*. However, memantine failed to modify cortisol levels in a trial in healthy volunteers *(80)*.

Other Agents Acting on Glutamatergic System

There are not many trials evaluating the action of glutamate-modulating agents on ACTH and cortisol release in humans. Magnesium ions exert NMDA antagonistic properties and magnesium was found to reduce the release of ACTH and to affect adrenocortical sensitivity to ACTH *(81)*. D-Cycloserine, a partial agonist of the glycine recognition site of the NMDA receptor failed to modify cortisol levels in healthy males *(82)*. In healthy volunteers, infusion of the dissociative anesthetic drug ketamine acting as a low-affinity NMDA antagonist resulted in increased cortisol levels *(80)*. This finding is in good agreement with the results of animal studies mentioned above. In a recent study *(83)*, supplementation with dehydroepiandrosterone known to have also glutamatergic properties, significantly increased vasopressin response to exercise. The authors speculated that the mentioned effect of the steroid could be mediated via enhanced NMDA excitatory activity. Similar trends were noted for ACTH and cortisol, but the marked variability precluded statistical significance.

Conclusion

The involvement of EAA in the control of ACTH release is well established. Glutamatergic regulation of ACTH release has a clear significance for the stress response and neuroendocrine functions during development. A dysregulation of the HPA axis has been reported in several psychiatric and neurological disorders, in which alterations of glutamatergic neurotransmission seem to play a pathophysiological role. So far, only fractional indices on the clinical importance of the interaction between EAA and ACTH secretion have been obtained in both preclinical and clinical studies (Table 1). However, modulation of HPA func-

tion by drugs influencing glutamatergic system seems to be a promising approach to future therapeutic strategies.

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