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The Emerging Role of Metabotropic Glutamate Receptors in the Pathophysiology of Chronic Stress-Related Disorders

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Abstract: Chronic stress-related psychiatric conditions such as anxiety, depression, and alcohol abuse are an enormous public health concern. The etiology of these pathologies is complex, with psychosocial stressors being among the most frequently discussed risk factors. The brain glutamatergic neurotransmitter system has often been found involved in behaviors and pathophysiologies resulting from acute stress and fear. Despite this, relatively little is known about the role of glutamatergic system components in chronic psychosocial stress, neither in rodents nor in humans. Recently, drug discovery efforts at the metabotropic receptor subtypes of the glutamatergic system (mGlu1-8 receptors) led to the identification of pharmacological tools with emerging potential in psychiatric conditions. But again, the contribution of individual mGlu subtypes to the manifestation of physiological, molecular, and behavioral consequences of chronic psychosocial stress remains still largely unaddressed. The current review will describe animal models typically used to analyze acute and particularly chronic stress conditions, including models of psychosocial stress, and there we will discuss the emerging roles for mGlu receptor subtypes. Indeed, accumulating evidence indicates relevance and potential therapeutic usefulness of mGlu2/3 ligands and mGlu5 receptor antagonists in chronic stress-related disorders. In addition, a role for further mechanisms, *e.g*. mGlu7-selective compounds, is beginning to emerge. These mechanisms are important to be analyzed in chronic psychosocial stress paradigms, *e.g*. in the chronic subordinate colony housing (CSC) model. We summarize the early results and discuss necessary future investigations, especially for mGlu5 and mGlu7 receptor blockers, which might serve to suggest improved therapeutic strategies to treat stress-related disorders.

Keywords: Animal models, anxiety, chronic stress, depression, mGlu receptors, stress-related disorders.

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THE GLUTAMATE SYSTEM IS IMPLICATED IN STRESS-RELATED PHYSIOLOGY AND DISORDERS

Major depression, anxiety, and drug abuse disorders represent the most prevalent stress-related psychiatric conditions and are an enormous health concern worldwide [1-3]. The etiology of these pathologies is complex, with chronic psychosocial stressors being the most acknowledged risk factors [1, 2, 4-8]. These factors include continuing adverse conditions, such as social decline along with poverty, or life events that possess a high degree of chronic threat (*e.g*. medical disabilities), long lasting negative emotions and experience of personal loss [5, 7-9]. The majority of these types of factors has been demonstrated to increase both anxiety- and depression-related behavior, but also alcohol and drug abuse [10-13]. Indeed, and not surprisingly, there's a high comorbidity between anxiety and depression/mood disorders, with approximately half of the patients suffering from major depression also meeting criteria for comorbid anxiety [14].

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As disorders of mood and emotion may show a common excessive or inappropriate brain excitability within crucial brain circuits, the L-glutamate system, which represents the primary excitatory neurotransmitter system in emotion and cognition circuits, is increasingly considered to play an important role in mental disease etiology and persistence. Several lines of evidence from human clinical studies link dysfunction in the L-glutamate system to the pathogenesis of psychiatric disorders [15]. For instance, changes in glutamate levels have been found in plasma, cerebrospinal fluid (CSF), and in the brain of patients suffering from mood and anxiety disorders [16-18]. Interestingly, recent postmortem studies showed significant increases in glutamate levels in the frontal cortex and dorsolateral prefrontal cortex of depressed and bipolar patients, respectively [19, 20]. Furthermore, various clinical neuroimaging studies have consistently demonstrated volumetric changes in brain regions, in which glutamatergic neurons predominate, such as the hippocampus, amygdala and several cortical regions [21].

The L-glutamate neurotransmitter system of the emotion and cognition circuitry of mammalian brains is composed of a large diversity of genetically regulated factors: a group of vesicular, glial and synaptic glutamate transporters [22] as well as two families of glutamate receptors: ligand-gated ionotropic glutamate receptors (iGlu) comprising (2R)-2-(methylamino)butanedioic acid (NMDA)-, 2-amino-3-(5-methyl-3-oxo-2,3-dihydro-1,2-oxazol-4-yl)propanoic acid

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(AMPA)- and (2S,3S,4S)-3-(carboxylatomethyl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylate (kainate, KA)-receptors [23-26], and the G protein-coupled metabotropic glutamate receptor (mGlu) subtypes -1 to -8 (mGlu1-8, [26-29]). Throughout the last three decades, several drug discovery efforts were made targeting iGlu receptors, with preclinical and clinical data demonstrating NMDA and AMPA receptors to be promising targets in controlling cognitive and emotional changes observed in stress-related disorders [30-33]. In this regard, a major breakthrough came from clinical studies using the NMDA receptor antagonist ketamine by showing clinical efficacy in treatment-resistant depression (TRD) and major depressive disorder (MDD) patients. Interestingly, ketamine administered intravenously showed strong decreases in the Hamilton Depression Rating Scale (HDRS) analysis, with an improvement observed 2 h after infusion that remained significant for more than 1 week [34, 35]. However, this iGlu receptor-based strategy is not devoid of limitations and risks, as ketamine administration has also been shown to be associated with cognitive and dissociative adverse effects, which thus limits ketamine's widespread application for the treatment of mood disorders [36, 37]. In contrast, therapeutic strategies targeting mGlu receptors represent a more subtle alternative in regulating excitatory (and possibly inhibitory) neurotransmission and are therefore considered to have a more favorable side-effect profile than ligand-gated ion channel modulation [38, 39]. Indeed, signaling *via* mGlu receptors is slower and longer lasting than *via* iGlu receptors, allowing fine-tuning of glutamate regulation and its cellular responses, which could eventually avoid the adverse effects associated with direct modulation of iGlu receptors. In addition to that, growing evidence gives rise to mGlu-based compounds to be effective in regulating iGlu receptor signaling, further emphasizing the modulatory potential of mGlu receptors.

By summarizing the findings from preclinical and recent clinical studies, the present review will illustrate the involvement of different mGlu receptor subtypes in the pathophysiology of stress-related emotional disorders. Here, we especially focus on the role of the different mGlu receptors in the development of depressive and anxiety disorders and largely neglect their role in somatic disorders and substance abuse, allowing us to go more into depth with respect to the former two. Moreover, we show that the discovery of selective ligands for these receptors created potentially new strategies for the therapy of psychiatric disorders and their comorbid somatic syndromes. We will summarize in detail the growing evidence for mGlu receptors to serve as promising molecular targets for the treatment of chronic stress-related disorders in man. We will first introduce animal models typically used to analyze acute and particularly chronic stress conditions on a preclinical basis. To this end, we compare different acute and chronic stress models and eventually focus on one distinct animal model that most appropriately mimics chronic psychosocial stress, the CSC model [40, 41]. Applying this preclinically validated model, we will also report on recent findings obtained by our group and others to provide first evidence for a role of mGlu subtypes in chronic psychosocial stress, which further emphasizes the importance of this receptor family as promising drug targets towards ensuring mental health.

GLUTAMATE SIGNALING *VIA* MGLU RECEPTORS IN THE CNS

The existence of neuromodulatory glutamate receptors, namely the mGlu receptors, provides a mechanism by which binding of glutamate, in contrast to the fast synaptic responses mediated by iGlu receptors, slowly modulates cell excitability, synaptic neurotransmission and plasticity; mGlu receptors perform this modulation *via* second messenger signaling pathways and their interactions with ion channels [26, 42-44]. According to sequence homology, second messenger coupling and pharmacological properties, the mGlu receptor family is subdivided into three groups. The group I members, mGlu1 and mGlu5, are coupled to $G_{q/11}$ proteins and primarily elevate {[(1R,2S,3R,4R,5S,6R)-2,3,5-trihydroxy-4,6-bis(phosphonooxy)cyclohexyl]oxy}phosphonic acid (IP_3), diacylglycerol (DAG), and Ca^{2+} signal transduction. In general, these receptor subtypes function to enhance glutamate-mediated postsynaptic excitation [38, 45-49]. In contrast, group II (mGlu2 and mGlu3) and group III (mGlu4, -6, -7, and -8) receptors inhibit adenylyl cyclase activity and other effector proteins *via* coupling to $G_{i/o}$ proteins and thereby negatively modulate excitatory neurotransmitter efflux and neuronal excitability upon activation [38, 50-55]. Interestingly, various mGlu receptors are expressed in both neurons and glial cells of the central nervous system (CNS), as well as in peripheral tissue like the enteric nervous system or adrenal gland cells [56]. In neurons, group I receptors show predominantly postsynaptic location and modulate cell excitability, while group II and III members are mainly expressed at the presynapse and are involved in regulating neurotransmitter release, mostly inhibiting release [57, 58]. As they are members of class C GPCR, all mGlus are characterized by a large extracellular N-terminal "Venus flytrap domain" (VFTD), which is known to serve as the orthosteric ligand binding site and shows abundant homology between the different mGlu receptor subtypes. The binding site for allosteric modulators of the mGlus is located topographically distinct within the transmembrane domain [59-64]. As the allosteric binding site has a higher level of sequence diversity between the receptor subtypes, allosteric ligands typically show greater subtype selectivity [65, 66]. Importantly, the widespread distribution of mGlu subtypes suggests that these modulatory receptors have the ability to participate in a broad array of physiological functions throughout the CNS and may represent suitable targets for therapeutic intervention in a variety of CNS disorders. Thus, the therapeutic potential of the mGlu receptors is increasingly receiving attention as possible treatment strategies for CNS diseases such as Parkinson's disease (PD), Fragile X syndrome (FXS), schizophrenia, addiction, and in particular depression and anxiety-related disorders [67-71].

Group I mGlu Receptors: Neurobiochemistry and Distribution

In general, the group I members mGlu1 and mGlu5 couple to $G_{q/11}$ proteins and activate phospholipase C, a process that results in the formation of IP_3 and DAG (see Fig. **1**). This classical pathway leads to intracellular Ca^{2+}

mobilization and activation of protein kinase C (PKC). Apart from this, group I receptors can also activate a range of further downstream effectors, most notably proteins involved in synaptic plasticity, such as mitogen-activated protein kinase/extracellular receptor kinase (MAPK/ERK) and mammalian target of rapamycin (mTOR) [72-74]. With respect to their distribution, expression of both mGlu1 and mGlu5 primarily overlaps within brain regions implicated in mood disorders [36]. However, there are also distinct differences, with mGlu1's expression being abundant in cerebellum, olfactory bulb, the CA3 region of the hippocampus, in thalamus, dentate gyrus and substantia nigra, whereas mGlu5 is highly expressed in telencephalic regions, CA1 and CA3 regions of the hippocampus, septum, basal ganglia, striatum, amygdala and nucleus accumbens [37, 75]. In addition, mGlu5 is also expressed in glial cells (see Fig. **1**), particularly in astrocytes, where its expression has been highlighted with respect to a number of potential physiological roles, *e.g.* neuroprotection [76-80].

Group II mGlu Receptors: Neurobiochemistry and Distribution

In contrast to group I, the group II members mGlu2 and mGlu3 are coupled predominantly to $G_{i/o}$ proteins negatively modulating adenylyl cyclase activity and directly regulating ion channels and other downstream signaling components *via* the release of the $G_{\beta\gamma}$ subunit. In addition, group II mGlus also couple to MAPK and phosphatidyl inositol 3- (PI3-) kinase pathways which are implicated in synaptic plasticity [39, 81, 82]. Both mGlu2 and mGlu3 are presynaptically localized in rather preterminal than terminal axonal portions, distant from the active zone of neurotransmitter release, where they are potentially activated by synaptic glutamate spillover [83]. mGlu2 mRNA is

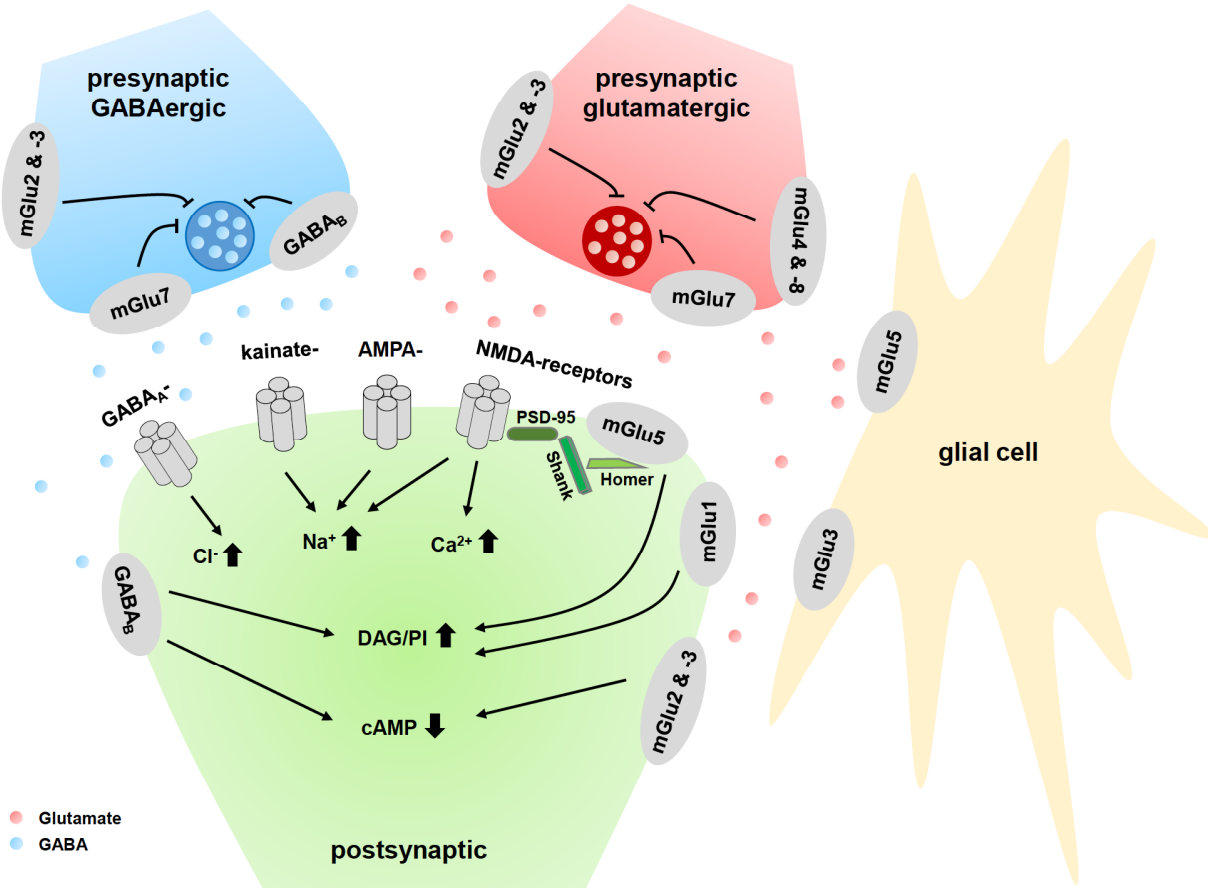

Fig. (1). Schematic representation of mGlu receptors at the synapse. In general, group I mGlu subtypes are localized postsynaptically, whereas group II and III receptors are localized mainly in presynaptic locations. While the mGlu7 receptor subtype is localized in the active zone, mGlu subtypes 2, 3, 4, and 8 are generally found in perisynaptic locations on the presynapse. Group II and III receptors modulate the release of glutamate (right, red circles) or 4-aminobutanoic acid, GABA (left, blue circles). At the postsynaptic terminal, the ionotropic (2R)-2-(methylamino)butanedioic acid (NMDA)-, 2-amino-3-(5-methyl-3-oxo-2,3-dihydro-1,2-oxazol-4-yl)propanoic acid (AMPA)- and (2S,3S,4S)-3-(carboxylatomethyl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylate (kainate, KA)-receptors respond to glutamate with increases in intracellular sodium or calcium, promoting cell excitability. Group I mGlus signal *via* $G_{q/11}$ proteins to increase diacylglycerol (DAG) and phosphatidylinositol (PI). Importantly, mGlu5 and NMDA receptors are closely linked to each other *via* Shank, Homer and PSD-95 (postsynaptic density-95) proteins. Postsynaptic mGlu2/3 and $GABA_B$ receptors couple to cAMP inhibition. Instead, $GABA_A$ chloride channels modulate intracellular chloride levels. Expression of mGlu3 and mGlu5 on glial cells has emerged as another key site for regulation of synaptic activity, however, the consequences of receptor activation on these cells and the exact signaling pathways are presently not well understood.

observed to be highly expressed in pyramidal neurons in the enthorhinal and parasubicular cortical regions and in granule cells of the dentate gyrus [84, 85]. In contrast, mGlu3 mRNA is highly expressed in neurons of the cerebral cortex and the caudate-putamen and in the granule cells of the dentate gyrus [86, 87]. In addition, the mGlu3 receptor subtype (see Fig. **1**) is also prominently expressed in glial cells throughout the whole brain, and its activation provides robust neuroprotection *in vitro* and *in vivo* [88-91].

Group III mGlu Receptors: Neurobiochemistry and Distribution

Group III represents the largest family of mGlu receptors and comprises the subtypes mGlu4, mGlu6, mGlu7, and mGlu8. Like group II, group III members are predominantly expressed presynaptically (see Fig. **1**) [92], where they regulate neurotransmitter release [28, 93-97]. By coupling to $G_{i/o}$ proteins, their activation inhibits cAMP formation and indirectly affects synaptic transmission and neurotransmitter release by modulating membrane Ca^{2+}- and K^{+}-channels [51, 55, 98]. As with group II mGlu receptors, the group III subtypes also couple to other signaling pathways, including MAPK and PI3-kinase, providing further complexity to the mechanisms by which they regulate synaptic transmission [99-101]. Except for the mGlu6 receptor subtype, whose expression is restricted to the retina, all other group III mGlus are widely expressed throughout the mammalian brain and also in peripheral tissue [37, 56]. In detail, in the CNS the mGlu4 receptor subtype is highly expressed in the cerebellum, the olfactory bulb and thalamus as well as in the hippocampus, the cerebral cortex and basal ganglia in pre- and post-synaptical position [92, 102, 103]. In addition, widespread peripheral mGlu4 expression has been shown also in the pancreas, adrenal glands and gastrointestinal tract [104-107]. The mGlu7 receptor is highly localized in the presynaptic active zone and abundantly expressed in brain regions such as neocortex, hippocampus, amygdala, locus coeruleus, thalamus and hypothalamus [108-110]. In the periphery, mGlu7 expression has been reported in the adrenal glands, the colon and stomach – among other areas [111-113]. The mGlu8 receptor is found predominantly in the CNS in presynaptic terminals in the olfactory bulb, hippocampus, cerebellum and cortical areas [75], but also in peripheral tissue such as pancreas and testis [56]. Interestingly, general expression levels of mGlu8 receptors seem considerably lower than those of mGlu4 and mGlu7 [39].

ESTABLISHED RODENT MODELS FOR THE EVALUATION OF STRESS

In general, "stress" can defined either as an activation of a stress response, a stressful stimulus itself, and/or the consequences of a stressful experience [114-119]. Undoubtedly, exposure to stress or even trauma (experience or witness of a terrifying event and difficulty in coping with it for a long time) has been shown to be amongst the predisposing factors for developing emotional disorders in man, such as depression and anxiety, which are often viewed as manifestations of an inability to cope with stress [2, 120, 121]. Albeit the biological basis of the stress response is not clearly defined, its understanding is essential for a better comprehension of the etiology of those disorders. Animal models have turned out to be instrumental in this respect and, like in humans, animals use coping strategies when exposed to stress. They can express both active coping mechanisms manifested by aggressive behaviors as well as exploratory activity or passive coping manifested by freezing, immobility and submission [122]. All these behaviors can be reliably measured in different animal models. In the following, various animal models are discussed in which the animal's stress response is reflected either upon exposure to acute or to chronic stress. Paradigms that employ acute stressor exposure include stress-induced hyperthermia (SIH), the forced swim test (FST), the tail suspension test (TST), elevated plus maze (EPM) and learned helplessness (LH), to name a few. On the other hand, chronic mild stress/chronic unpredictable stress (CMS/CUS), chronic social defeat stress (CSDS) and chronic subordinate colony housing (CSC) represent chronic stress models, all of which employ relatively long-term exposure to inescapable or uncontrollable stress events.

Assessment of Acute Stress in Rodent Animals

The SIH Test

In general, SIH is known to be a physiological phenomenon when a mammalian organism is confronted with an either physical or psychological stress situation [123-127]. In the SIH test, modified from the version originally described by Borsini *et al.* [128], the basal temperature is measured rectally (T1), followed by a second rectal measurement 15 minutes later (T2). During these 15 minutes the temperature usually rises due to physical stress the animal is undergoing (handling, rectal measurement). Conveniently, potential anxiolytic-like effects of drugs are measured by a decrease in the SIH response [125]. Those measurements of the body temperature are not dependent on the animal's motoric activity, which makes SIH different from other mild stress models/anxiety tests that depend on locomotor performance of the animal, for instance the EPM or open field tests.

The FST and TST

The FST and TST are the two most widely used preclinical screening tests that allow rapid detection of substances with potential antidepressant-like activity (good predictive validity). In general, both tests are based on the same principle, which is the measurement of the duration of immobility while rodents are exposed to an acute, short-term (minutes) inescapable situation. In the FST, first described by Porsolt *et al.* [129, 130], a mouse or a rat is placed in a water-filled cylinder, in which the animal is unable to escape from. Following an initial period of escape-oriented movements, the animal will eventually display an immobile posture, a passive behavior characterized by the absence of movements except those necessary to keep the head above the water level. By contrast, in the TST, immobility is scored while mice are suspended by their tails and, as water is not required, this test is not confounded by challenges of thermoregulation [131]. In both tests, the immobility is typically interpreted as an expression of behavioral despair

[132-134], which can be reversed by the acute administration of compounds with antidepressant potential. So, testing of new substances in these stress models allows a simple and rapid screening of potential antidepressant activity by the measurement of their acute effect on immobility. However, this poses a problem for the model, as antidepressants used in depressed humans in the clinics generally require many weeks of administration to elevate mood. Nevertheless, both, the FST and TST are currently popular models, mostly due to their low cost of experiments, their ease of use and their reliability across laboratories [127, 135].

The EPM Test

The EPM represents one of the most widely used anxiety models, in which anxiety is typically measured by indices of open-arm avoidance and locomotion by the frequency of closed-arm entries [136, 137]. In principle, this test exploits the balance between the preference of rodents for avoiding open exposure to potential predators *versus* exploration for possible rewards. When placed in the center portion of the plus-maze and allowed to explore each of the arms freely, mice with higher anxiety will show reduced open-arm activity and *vice versa*. This tendency can be, for instance, suppressed by anxiolytics and potentiated by anxiogenic agents [138]. As short-term exposing of animals to heights and bright open spaces demonstrates an acutely stressful situation, the EPM can also be used and interpreted as a test for mild stressor exposure [139, 140].

The LH Model

The LH model can be basically viewed as analogous to the abovementioned tests, with the difference that it involves a series of stressors over a few hours or even days [141]. Following an uncontrollable stressor such as exposure to inescapable electric foot shocks, animals eventually will either display increased escape latency or completely fail to escape from a subsequent situation in which escape is possible [142-144]. Importantly, the escape deficits can be reversed by a variety of antidepressants [145]. Following one or more sessions of inescapable shock, animals have been shown to develop persistent changes that are reminiscent of depression, including weight loss, alterations in sleep pattern, hypothalamic-pituitary-adrenal (HPA) axis activity and loss of spines in hippocampal regions [131, 146, 147]. The attractiveness of LH is that the model is based on the consideration that cognitive functions (*e.g.* learning) are linked to other behavioral outcomes (*e.g.*, neurovegetative modalities), and thus, this model helps to provide a reasonably integrated and broad picture of depressive symptomatology that are analogous to the human situation. However, the major drawback of the model is that most of the depression-like symptomatology does not persist beyond 2-3 days following cessation of the uncontrollable shock. Moreover, another limitation is – in contrast to the FST and TST - the difficulty to replicate between laboratories, particularly in mice. Until today, these acute stress models clearly represent the first line of behavioral tests used to rapidly screen putative antidepressant and anxiolytic compounds and to phenotype transgenic animals. Even though direct links to emotional disorders in man are obviously weak due to utilizing only acute stressors and testing only acute antidepressant/anxiolytic responses, these acute stress models have helped enormously to reveal important molecular players within the CNS emotion circuitry [148-151].

Chronic Mild Stress (CMS), Chronic Social Defeat Stress (CSDS) and Chronic Subordinate Colony Housing (CSC)

While acute stress paradigms are used broadly for their ease, automation potential, and rapid phenotyping abilities, they offer singular readouts that often cannot be unambiguously interpreted. For instance, increased immobility in the FST is often interpreted as an expression of despair. However, it can also be understood as a successful and adaptive behavioral response that functions to conserve energy [152]. Today's chronic stress models are distinguished by their remarkable ability to simultaneously produce a set of behavioral alterations with strong face validity for depression and anxiety disorders (behavioral manifestations that should be similar to the symptoms observed in affected humans). Based on the clinical evidence that chronic stress significantly increases pathogenesis of affective diseases, these stress models are potentially of high value to better understand the underlying physiological mechanisms [41, 148]. Basically, they are composed of repeated and/or permanent applications of an uncontrollable and unpredictable stressor that is associated with quantifiable molecular, behavioral and physiological changes.

The CMS Model

In the CMS model, also referred to as chronic unpredictable stress (CUS) paradigm [153, 154], rodents are exposed to a variety of relatively mild, mostly physical, stressors such as restraint, isolation housing, disruption of light-dark cycles, intermittently for relatively prolonged time periods (*e.g.* several weeks). Typically, a variety of stressors is used within the CMS schedule in order to prevent or delay habituation, which can occur rapidly when a single stressor is presented repeatedly [153, 154]. In addition to a reduction in sucrose preference [155], CMS has also been shown to result in a number of other changes that are difficult to objectively quantify, such as grooming deficits and changes in aggressive and sexual behavior. Interestingly, however, many of these changes can be reversed by chronic antidepressants applied either during the stress procedure or as a post-stress treatment [156, 157]. However, as the CMS model only employs physical stressors and often lacks cross-laboratory reliability, other approaches to develop chronic psychosocial stress-based models, more reminiscent of human depression, have emerged in recent years.

The CSDS Model

The stress models described above are based exclusively on physical stressors, and thus, are lacking the relevance of mimicking most important situations that human beings encounter in everyday life – i.e. social interactions [158-161]. As opposed to CMS, the CSDS model clearly includes an important social stress component, and thus displays remarkable strength as it relies on innate social behavior. The model is based on the principle that two animals interact socially and physically such that one achieves dominant status and the other becomes subordinate. Much of the

preclinical aggression research has been conducted so far in territorial male resident rats or mice confronting an intruder conspecific. As a consequence of territoriality, the resident will attack unfamiliar males intruding in its home cage. However, there are many versions of CSDS for mice and rats. For example, a typical procedure in mice lasts for 21 days where the experimental animal is (repeatedly) exposed to 10 intermittent bouts (5-10 min, once daily; see Fig. **2 A**) of social defeat. Here, the experimental mice are forced to intrude into cage space occupied by a larger mouse of a more aggressive strain, leading to subordination of the experimental mice. In addition to the short-time physical stress during direct contact with the dominant male, the experimental mice are exposed to additional psychological stress in form of prolonged "not physical" contact by housing them for 24 h in the same cage as the residents, but with a transparent partition allowing only sensory interaction [162, 163]. Other laboratories expose the experimental mice also daily to 10 min of physical interaction with a resident followed by 24 h of sensory contact, but only for 10 consecutive days [164-166]. For rats there are protocols where the experimental animals are placed in a resident's home cage for 5 min physical interaction, followed by 10 min of sensory threat for 4 consecutive days [167, 168], or where the intruders are placed in the cage of the resident for intermittent physical interaction until submission, followed by 30 min of sensory threat for 1 to 3 consecutive days [169-171]. Although there are many more versions and mentioning all of them would go beyond the scope of this article, following repeated exposure to a dominant encounter,

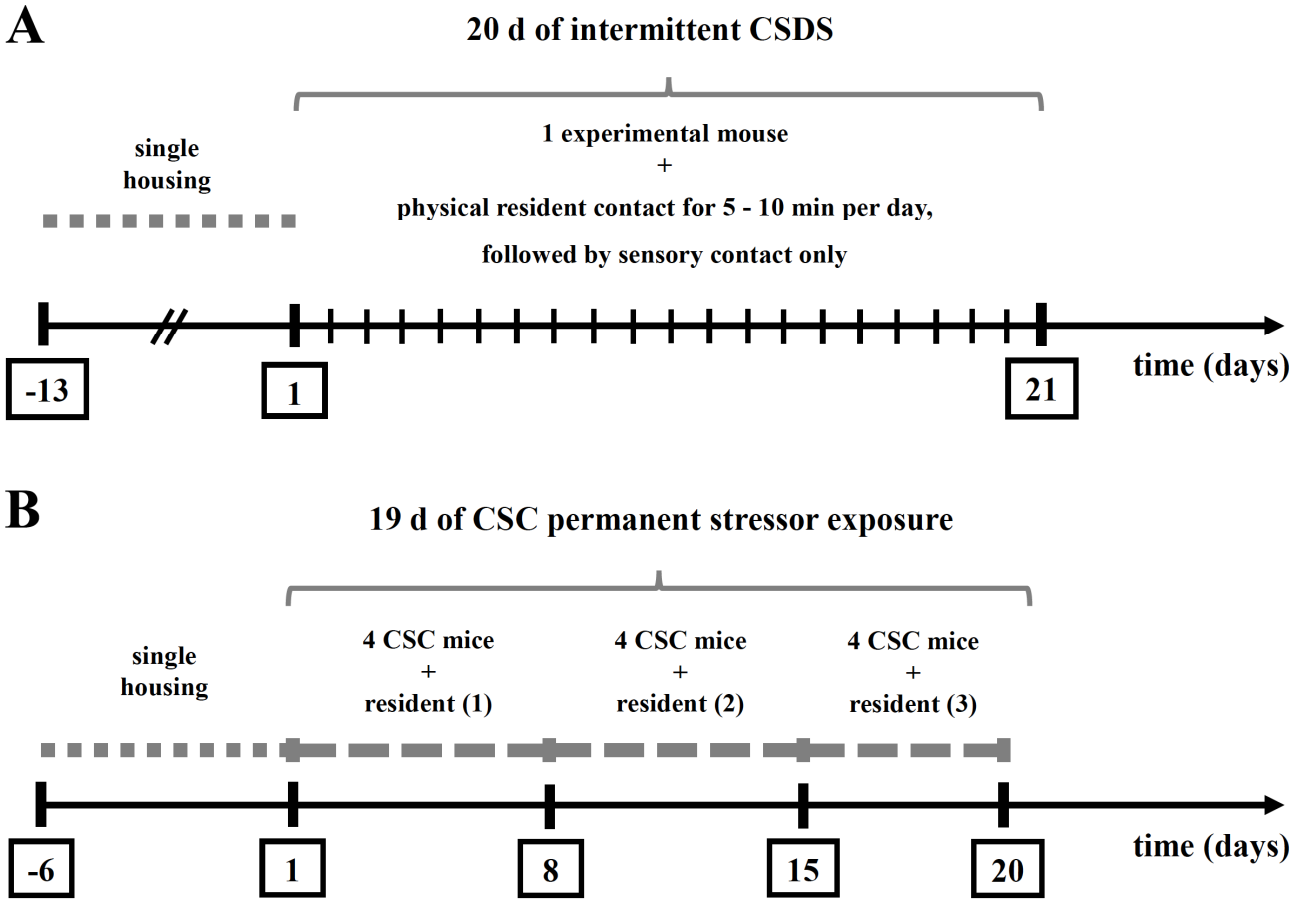

Fig. (2). Schematic illustration of the experimental design of the chronic social defeat stress (CSDS) (A) and the chronic subordinate colony housing (CSC) (B) paradigms in mice. (A) In this CSDS procedure, which lasts for 21 days, experimental animals are introduced to a larger male resident mouse until defeat is achieved. Subsequently, the animals spend 24 h in the same cage, only divided by a holed metal or transparent partition, which only allows sensory but no physical contact. Stressed animals are exposed to a new resident every day to minimize a potential habituation effect. Control mice remain single-housed and unstressed in their home cages for the course of the experiment. Typically, during the last week of the paradigm, all behavioral tests are performed (OF, EPM test, acute stress response test; see [162, 163]). (B) In the CSC paradigm, male mice weighing 19-21 g are housed singly for one week before they are assigned to the single-housed control (SHC) or the CSC group in a weight-matched manner. In order to induce chronic psychosocial stress, CSC mice are housed together with a larger dominant male for 19 consecutive days. In detail, four experimental CSC mice are put into the homecage of resident (1) on day 1 of CSC, resulting in immediate subordination of the four intruder CSC mice. The latter are then housed together with this dominant resident (1) for 7 consecutive days. On day 8, and again on day 15 of CSC, the four experimental CSC mice are transferred into the homecages of resident (2) (day 8) and resident (3) (day 15), respectively, in order to avoid habituation. On day 19, CSC and SHC mice are usually tested for their innate or physiological anxiety and on day 20 immunological and physiological parameter are assessed.

independent of the protocol used, animals reliably show decreased sucrose preference, indicative of an anhedonia-like state, and show reduced social interaction/sociability, as well as alterations in HPA axis and autonomic function [172-174]. Importantly, many of these changes can be reversed by chronic, but not acute, antidepressant drug administration, illustrating pharmacological validity of this stress model [175-177].

The CSC Model

The CSC paradigm was established by Reber *et al.* [40] and represents a chronic psychosocial stress model with similarities to the CSDS model, but with the difference of applying psychosocial stress not only intermittently but permanently over a period of 19 days (24 h per day; see Fig. **2 B**). This chronic stress model is a very reliable animal model in combining chronic, psychological and social aspects of stress. In doing so, and as compared to the other stress models of above, it more comprehensively mimics the type of health compromising stressors that humans are exposed to. Typically, four male mice are housed together with a larger male resident in its homecage for 19 consecutive days. This results in immediate subordination of the four intruder CSC mice, and a hierarchy within each colony is formed, in which the resident clearly obtains the dominant position. To avoid habituation to the dominant mouse, the four CSC mice are transferred into the homecage of a novel larger male resident mouse on days 8 and 15. Single-housed (SHC) mice that remain undisturbed serve as unstressed controls [178]. Importantly, studies by the group of Reber clearly demonstrate that CSC stressor exposure leads to the development of affective, immunological and somatic changes and also results in reduced glucocorticoid (GC) signaling (see Fig. **3**, [41]), and thus provides a powerful experimental tool to study the mechanisms underlying several relevant stress-induced conditions. In detail, is has been shown that exposure to CSC alters several parameters indicative of chronic stress, including reduced body weight gain, decreased thymus weight and increased pituitary and adrenal weight [40, 140]. The latter finding is accompanied by a reduced responsiveness of adrenal explants to adrenocorticotropic hormone (ACTH) challenge *in vitro*. Importantly, adrenal ACTH sensitivity seems to be not only diminished under *in vitro* conditions, as CSC mice show unaffected basal morning plasma corticosterone (CORT) despite elevated plasma ACTH levels in comparison with SHC mice. Moreover, CSC mice show basal evening hypocorticism, suggested by decreased basal evening plasma CORT levels compared with SHC mice [40, 140, 179]. The decline in GC signaling is further amplified by a reduced GC sensitivity seen in lipopolysaccharide-stimulated splenocytes [40] and plate-bound anti-CD3-stimulated T helper (Th) 2 cells from peripheral lymph nodes [180] of 19-day CSC compared with SHC mice. These are interesting findings, as an insufficient GC signaling can be observed in numerous affective and somatic disorders in man following chronic psychosocial stressor exposure [181-184]. In addition, CSC-stressed mice develop a spontaneous colonic inflammation, indicated by an increased secretion of proinflammatory cytokines from mesenteric lymph node cells *in vitro* and an increased histological damage score of colonic tissue [40, 185, 186]. Moreover, CSC exposure was also shown to increase the risk for the development of inflammation-induced colorectal cancer (CRC), indicated by the development of macroscopic suspect lesions, as well as a trend towards an increased incidence of low- and/or high-grade colonic dysplasia [186]. Interestingly, in humans, inflammatory bowel disease (IBD) has been shown to be a consequence of chronic life stress and colorectal cancer poses one of the most serious complications in these patients [187-191]. Furthermore, IBD was also shown to be comorbid in patients suffering from depression [192-194]. These findings further indicate that the CSC paradigm is an appropriate model of chronic psychosocial stress with high construct validity (i.e. high disease relevance of methods by which the animal model is constructed; [141]).

With respect to their behavior, CSC mice show reduced open-arm activity on the EPM and reduced center-activity in an open field after 19 days of CSC, further illustrating that chronic stressor exposure increases anxiety-related behavior, a phenomenon that co-occurs with depression in humans [14]. Moreover, CSC mice spend a similar time investigating an empty cage and a cage with an unknown conspecific during the social preference/avoidance test (SPAT) on day 20 of CSC, suggesting a lack of social preference [195]. In addition, CSC mice also show an increased ethanol (EtOH) preference and total intake, which was already shown following 14 days of CSC exposure [196]. Interestingly, in humans chronic psychosocial stress represents a strong risk factor for the development of substance abuse such as alcoholism, which is often co-morbid with anxiety disorders [197-199].

Taken together, the CSC paradigm represents an animal model that utilizes a chronic psychosocial stress component and results in decreased GC signaling and concomitant affective and somatic pathologies, in particular the stress-induced anxiogenic phenotype and the systemic proinflammatory phenotypes. Thus, the CSC model is likely to have more translational value than other stress models in animals, *e.g.* when compared to the CMS or CSDS model, which lack either social or truly chronic components. Most interestingly, CSC exposure is associated with hypocorticism, a phenomenon that is not apparent after CMS or CSDS, but occurs in human mood disorders. In contrast, CMS and CSDS are associated with greatly elevated plasma CORT levels (hypercorticism). Interestingly, in addition to mice, the CSC paradigm was also established in rats [200]. However, to date the effects of CSC exposure in rats are not that well characterized as compared to mice. Overall, the CSC paradigm is a promising animal model that makes it also possible to gain further insight into how stress-induced pathophysiological changes (*e.g.* HPA axis alterations) eventually lead to affective and somatic disorders.

Taken together, the rodent models explained above can be performed in mice as well as in rats and which species to use probably depends on the particular research question to be answered. However, in case of the CSC model, mice will be the choice for future projects to gain more knowledge about the role of the brain glutamatergic neurotransmitter system in the development of affective and somatic changes, as the effects of chronic psychosocial

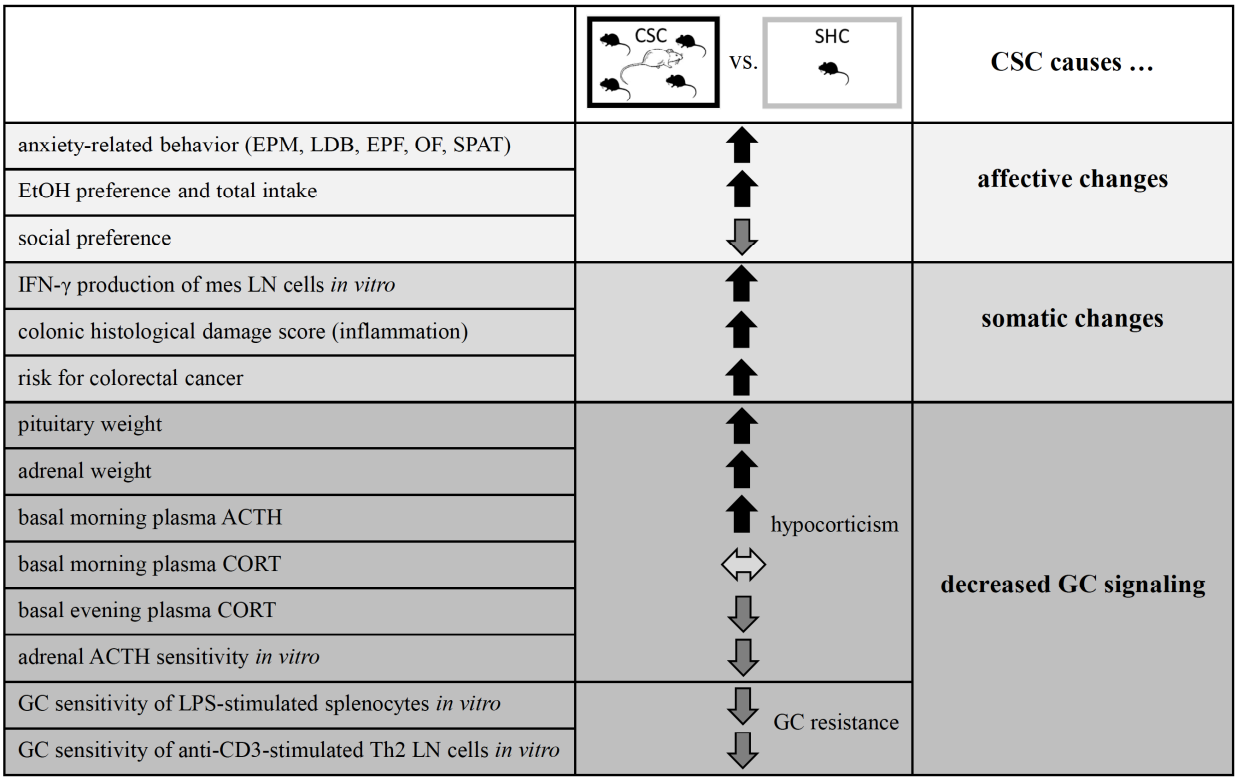

Fig. (3). Summary of the main effects of chronic psychosocial stress in male mice induced by 19 days of chronic subordinate colony housing (CSC) on behavioral, immunological and physiological parameters. Compared with single-housed controls (SHC), CSC mice show affective and somatic changes and develop decreased glucocorticoid (GC) signaling. Thus, the CSC paradigm represents a promising animal model to mimic diseases in which decreased GC signaling is a core feature and to unravel the underlying mechanisms of stress-related pathology in humans. Abbreviations: EPM, elevated plus-maze; LDB, light-dark box; EPF, elevated platform; OF, open field; SPAT, social preference/avoidance test; mes LN cells, mesenterial lymph node cells; ACTH, adrenocorticotropic hormone; CORT, corticosterone; LPS, lipopolysaccharide; Th2, T helper 2; adapted from [41].

stressor exposure using this model are much better characterized and robust in mice. Other advantages of mouse models are lower costs and less space necessary. Moreover, mouse models also offer the possibility to use transgenic animals, *e.g.* knockout mice, in order to analyze the underlying mechanisms.

Dysregulation of Brain mGlu Receptor Gene Expression after CSC Stressor Exposure and in Related Models

Recent findings clearly have sparked interest in neurobiological systems that were previously little explored in mood disorders, such as the glutamatergic system. In particular the clinical findings with ketamine have inspired new lines of preclinical research to explore the glutamate system in more detail, including modulatory receptors that could be targeted to achieve better side-effect profiles [201], and to investigate the underlying neural mechanisms. To our knowledge, only few studies have dealt with chronic stress and the involvement of mGlu receptors in the manifestation of stress-induced changes. But some promising results have already emerged. Wieronska *et al.* [202] addressed changes of mGlu5 expression in response to CMS exposure and reported an increase of mGlu5 protein expression in CA1 and a decrease in CA3 of the rat hippocampus. Furthermore, O'Connor and co-workers [203] found no changes of hippocampal group III mGlu receptor mRNA expression upon either chronic immobilization stress or chronic social defeat and concluded that hippocampal group III mGlu receptors may not be involved in the manifestation of behavioral and physiological changes observed in these models. However, early-life stress, which was induced by maternal separation, specifically reduced the expression of mGlu4 mRNA in the hippocampus, whereas mGlu7 and mGlu8 mRNA remained unaffected [204]. Taken together, they could demonstrate that there were only very few, but selective changes to group III mGlu receptors under early-life stress conditions. These findings ask for further research efforts to study mGlu receptors as potentially important players in chronic stress-induced pathology.

To extend and specify the range of these findings, we evaluated the molecular changes that occur within the mGlu receptor system upon chronic psychosocial stressor exposure in mice using the CSC animal model. We investigated the consequences of chronic psychosocial stress on gene expression of distinct mGlu receptor subtypes in several brain regions. Indeed, we found that mGlu7 mRNA was downregulated in the prefrontal cortex (PFC) of CSC mice (see Fig. **4**), suggesting that the mGlu7 receptor subtype is potentially involved in PFC-mediated emotional and/or cognitive processes that could be altered by CSC exposure. It

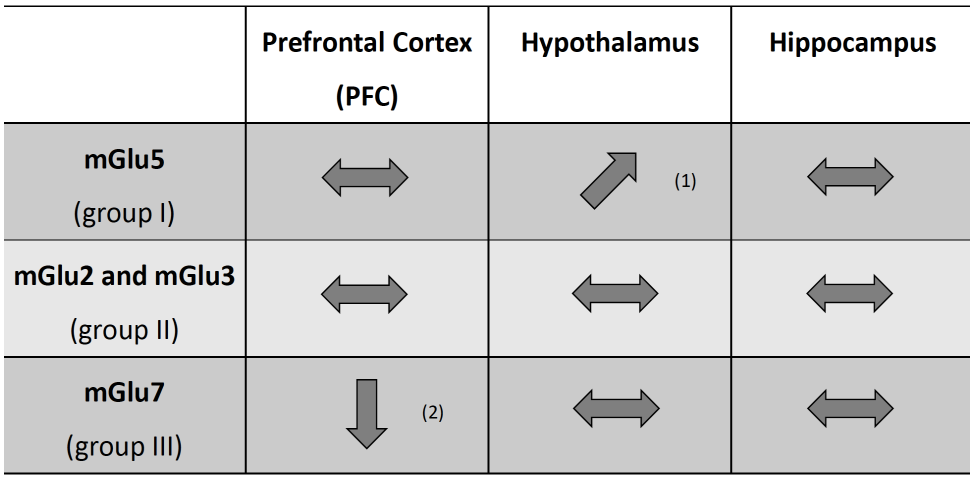

Fig. (4). Changes in relative gene expression of distinct mGlu receptors in three different brain regions (PFC, hypothalamus and hippocampus) that occur in response to 19 days of chronic subordinate colony housing (CSC). As a representative for group I, mGlu5 mRNA, for group II, mGlu2 and mGlu3 mRNA, and for group III, mGlu7 mRNA regulation was assessed relative to expression of the housekeeping gene glyceraldehyde 3-phosphate dehydrogenase (GAPDH) in comparison to respective SHC mice (set at 100%). Total RNA was isolated using Trizol reagent according to the manufacturer's instructions (Peqlab, Erlangen, Germany). RNA was re-suspended in 20 µL of RNase free water and its concentration and quality were analyzed spectrophotometrically (NanoDrop Spectrophotometer, Peqlab, Erlangen, Germany). cDNA was prepared from 500 ng of total RNA in a 20 µL final reverse transcription reaction mixture (using Superscript III; Invitrogen, Karlsruhe, Germany). Quantitative PCR was performed using the SYBR® Green Master Mix on an ABI 7500 Fast Sequence Detection System (Applied Biosystems, Darmstadt, Germany), with a thermocycler profile of 95°C (20 sec), followed by 40 cycles of 95°C (3 sec), 60°C (30 sec). Amplification of mGlu2, mGlu3, mGlu5 and mGlu7 receptor cDNA was carried out employing the following primers. mGlu2-forward: 5'-CGTGTCCGTCAGCCTCAGT-3', mGlu2-reverse: 5'-TGGCTCACCACGACGTTCTTCTG-3'; mGlu3-forward: 5'-TGTGATGGTGTCTGTGTGGCT-3', mGlu3-reverse: 5'-GTTTCCCGCTTCTCTGGCA-3'; mGlu5-forward: 5'-TGTGTACCTTCTGCC TCATTGC-3', mGlu5-reverse: 5'-GGAGAGAGACCGATGCCAATT-3'; mGlu7-forward: 5'-GCAGAAGGAGCCATCACCAT-3', mGlu7-reverse: 5'-GTCCGGGATGTGAAGTAAGCA-3'; GAPDH-forward: 5'-TGTGTCCGTCGTGGATCTGA-3', GAPDH-reverse: 5'-CCTGC TTCACCACCTTCTTGA-3'. Samples were prepared in triplicates and changes in gene expression were determined with the $2^{-\Delta\Delta CT}$ method [210]. Arrows indicate either no change (⇔), downregulation (⇩) or upregulation (⇗) of relative gene expression of respective mGlu mRNA levels in CSC compared to SHC mice. Student's *t*-test, following *p*-value determination: (1); $p = 0.07$, increase from 100% (SHC) to approximately 180% (CSC). (2); $p < 0.03$, decrease from 100% (SHC) to approximately 50% (CSC).

is interesting to note that mGlu7 receptors are also located on GABAergic neurons, on which they negatively regulate release of this inhibitory neurotransmitter. It is possible that the stress-induced reduction of mGlu7 mRNA levels potentially lead to enhanced excitatory transmission in the PFC, which may be part of the pathology observed in depression disorders [205]. Furthermore, we showed that mGlu5 mRNA was upregulated in the hypothalamus (see Fig. **4**), possibly suggesting that the mGlu5 receptor subtype is rather associated with mediating functionalities of the HPA axis' responses to CSC, which is consistent with mGlu5's postulated roles in physiological stress-regulation systems in mammals [206-209]. Interestingly, no CSC stress-induced changes were found in either mGlu2 or mGlu3 mRNA in neither brain region investigated (PFC, hypothalamus, or hippocampus; see Fig. **4**), possibly indicating that group II mGlu receptors may play a less prominent role in CSC-induced pathophysiology. Overall, the results discussed here represent very early evidence towards a role of mGlu receptor subtypes in chronic stress-induced pathophysiology. At least, our data suggest that there is possibly a controlling role of the mGlu7 receptor in the PFC and of the mGlu5 receptor subtype in the hypothalamus, indicating that these receptor subtypes should be pursued as further research topics in chronic stress-induced conditions. Of course, much future work is required to fully elucidate the roles these receptor subtypes play in chronic stress-induced behavioral and physiological symptomatology (see below).

CURRENT KNOWLEDGE OF MGLU RECEPTOR GENETIC AND PHARMACOLOGICAL MODULATION IN ACUTE AND CHRONIC STRESS

A possible aim of pharmacological intervention targeting glutamate neurotransmission in stress-related disorders could be that excessive glutamate exposure in specific brain areas should be blocked, whereas normal glutamatergic neurotransmission should be kept unaffected. New ways of fine-tuning the glutamatergic system are now emerging *via* the pharmacological modulation of mGlu receptor subtypes [36, 37, 58, 211]. The wide functional diversity and distinct distribution patterns of mGlu receptor subtypes provide an opportunity for selectively targeting individual mGlu subtypes in order to attempt the development of novel treatment strategies for emotional disorders. A large body of preclinical studies suggests that ligands for specific mGlu subtypes have potential in multiple mood disorders, including anxiety disorders and depression (Table **1**). More recently, data from clinical studies with mGlu subtype-selective ligands are beginning to emerge and are providing remarkable clinical efficacy of some of these compounds, which we discuss below.

Role of Group I mGlu Receptors in the Physiology of Stress

Group I mGlu receptors are broadly distributed within the peripheral and central nervous system and are expressed at post- and perisynaptic sites in several areas implicated in anxiety and emotional processing, and there is evidence for the involvement of these receptors in the pathophysiology of different emotional and somatic disorders. For example, human post-mortem studies reported specific reductions of total mGlu5 protein and mRNA levels in the lateral cerebellum [212, 213] and prefrontal cortex [214] in MDD patients [215]. Furthermore, a study by Wieronska *et al.* [202] showed an increase of mGlu5 expression in CA1 and a decrease in CA3 of rat hippocampus in response to CMS, an animal model showing symptoms related to human depression, supporting the involvement of mGlu5 in the pathophysiology of mood disorders in response to chronic stress.

Very interestingly, the mGlu5 receptor subtype is known to functionally interact with NMDA receptors by indirect physical and positive feedback linkage *via* a variety of intracellular mechanisms, including Homer, Shank and PSD-95 proteins [163, 216-221] (see Fig. **1**). This close functional association and positive reciprocal regulation between mGlu5 and NMDA makes the mGlu5 receptor subtype an attractive target for the indirect modulation of NMDA receptor function, which is known to be dysregulated in a variety of neuropsychiatric pathologies including mood disorders [222-225]. Importantly, as pharmacological activation of mGlu5 is shown to cause neurotoxicity and neurodegeneration [80, 226, 227], the activating mode of action will not be considered in the context of mGlu5's potential therapeutic application. In contrast, pharmacological blockade of mGlu5 function has emerged to be one of the most promising and quite advanced therapeutic strategies for the treatment of psychiatric conditions [163, 228-233]. This approach has demonstrated anti-stress efficacy in a number of animal and human studies. For instance, 3-(3-chlorophenyl)-1-(1-methyl-4-oxo-5H-imidazol-2-yl)urea (fenobam), a compound shown to be a clinically active anxiolytic already in the early 1980s [234, 235], was more recently described to exert its pharmacological effects *via* inverse receptor agonist activity at the mGlu5 receptor [236]. Moreover, allosteric blockade of mGlu5 with the prototypical allosteric receptor antagonist 2-methyl-6-(2-phenylethynyl)pyridine (MPEP) showed broad anxiolytic and antidepressant-like profiles in acute rodent animal models [237-241]. Li *et al.* [239] reported that administration of MPEP and the tricyclic antidepressant (TCA) imipramine resulted in a synergistic antidepressant-like effect in the FST and that this effect was even persistent after sub-chronic treatment (once daily, for five consecutive days). A further study revealed that MPEP remained equally active in reducing the SIH response in mice after sub-chronic dosing for five consecutive days, with comparable efficacy as after acute administration [242]. Those studies provided the first evidence that longer-term administration of mGlu5 blockers may have the potential to ameliorate stress-induced pathophysiology. Moreover, MPEP's anxiolytic activity could be confirmed in a battery of further acute animal models, such as the EPM, Vogel conflict- and marble burying-tests and the fear-potentiated startle paradigm [237, 238, 243-245]. Another selective mGlu5 receptor antagonist, 3-[2-(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP), turned out to be a good pharmacological tool to confirm anti-stress activity in several behavioral models [72, 246-250]. MTEP showed activity in the FST, TST and olfactory bulbectomy (OB) model [251, 252]. In the latter, repeated administration of MTEP attenuated the OB-related hyperactivity of rats in the open field test, a finding that resembles the action of typical antidepressants in the OB model of depression [252]. Obviously, both MPEP and MTEP have been studied in a wide range of preclinical animal models for different therapeutic indications, however, both compounds are not suitable drug candidates for clinical development due to pharmacokinetic constraints [253]. Beside the above mentioned, acute administration of the recently discovered mGlu5-selective negative allosteric modulator (NAM) 2-{2-[2-(difluoromethoxy)-5-({5H,6H,7H-pyrrolo[3,4-b]pyridin-6-yl}carbonyl)phenyl]ethynyl}pyridine (GRN-529) showed dose-dependent efficacy across a broad battery of animal models including the FST and TST, in anxiety tests (attenuation of SIH response and increased punished crossings in the four plate test) and in pain models (reversal of hyperalgesia due to sciatic nerve ligation or inflammation) [254]. Another novel and highly selective mGlu5 receptor antagonist, methyl (3aR,4S,7aR)-4-hydroxy-4-[2-(3-methylphenyl)ethynyl]-3,3a,5,6,7,7a-hexahydro-2H-indole-1-carboxylate (AFQ056, mavoglurant), showed an improved pharmacokinetic profile in rodents and better efficacy in SIH tests in mice as compared to the prototypic mGlu5 antagonist MPEP [255]. Interestingly, efficacy of AFQ056 has been reported also in L-dopa induced dyskinesia in Parkinson's disease and Fragile X syndrome in proof-of-principle clinical studies [255-258]. The mGlu5-selective NAM 2-chloro-4-{[1-(4-fluorophenyl)-2,5-dimethyl-1H-imidazol-4-yl]ethynyl}pyridine (basimglurant) turned out to be very promising in a phase II clinical study by demonstrating efficacy and safety as an adjunctive therapy in MDD patients using multiple read-outs. For instance, this study showed that a 6-week double-blind treatment of basimglurant versus placebo reached significant improvements in patient-rated Montgomery-Asberg depression rating scale (MADRS) results, in remission assessment and further ratings [231, 233, 259]. The consistency of the efficacy findings combined with good tolerability warrants further investigation with basimglurant in depressive disorders. Furthermore, the recently discovered mGlu5 NAM 2-chloro-4-[2-[2,5-dimethyl-1-[4-(trifluoromethoxy)phenyl]imidazol-4-yl]ethynyl]pyridine (CTEP), a compound chemically derived from basimglurant and optimized for utility in rodent studies, was shown to be active in acute rodent models, such as the SIH in mice and the Vogel conflict test in rats [228]. CTEP is the first reported mGlu5 inhibitor with both, very long half-life of approximately 18 h and high oral bioavailability in rodents, classifying as useful pharmacological tool for long-term treatment. CTEP thus allows the exploration of the full therapeutic potential of mGlu5 inhibition for indications requiring chronic receptor blockade. Indeed, Michalon *et al.* [229, 260] found out that chronic treatment with CTEP in a mouse model of Fragile X

rescued learning and memory deficits, elevated locomotor activity and increased spine density, suggesting that this mGlu5 NAM treatment may be effective in correcting multiple neurological symptoms [233]. Furthermore, a more recent study reported that chronic administration of CTEP was able to improve various behavioral alterations induced by chronic social defeat stress, such as reduced locomotion and an anhedonic phenotype [163]. Importantly, studies using mGlu5-deficient mice elegantly support the functional roles of mGlu5 in anxiety- and depression-related behaviors [239, 245].

One can speculate that these beneficial effects of mGlu5 blockade may result from a combination of different neurophysiological mechanism. First, disruption of thalamic-lateral amygdala long-term potentiation is observed with intra-amygdala injection of MPEP [261], which is a likely mechanism for the reduced acquisition of learned fear observed with MPEP in conditioned anxiety paradigms [261, 262]. Second, interference with hippocampal mGlu5 function and possibly dysregulation of expression by allosteric mGlu5 antagonists are also likely to contribute to anxiolytic activity [58, 263]. Third, mGlu5 blockade is known to interfere with functional parameters of the HPA axis, which represents the principal stress-response and -regulation system in mammals [206-208, 264]. Taken together, the reported findings substantiate the hypothesis that mGlu5 receptor antagonism is associated with anxiolytic and antidepressant-like effects and that this approach represents one of the most promising and advanced mGlu receptor strategies towards future treatment of chronic stress-related disabilities such as mood disorders.

Modulation of the second group I receptor, mGlu1, has originally been considered also as an attractive target for the treatment of anxiety. For instance, anxiolytic-like activities of mGlu1 receptor antagonists have been documented in various animal models, including, for example, the Vogel conflict- and SIH test [265-269]. Several other studies have also illustrated effects of mGlu1 receptor antagonists on fear memory [270-273]. However, as compared to mGlu5, the mGlu1 receptor subtype has been evaluated much less in the context of emotion, stress physiology and behavior, which may be due to reports on cognitive dysfunctions in mice lacking mGlu1 [274-276] or potentially induced by mGlu1-selective antagonist [266, 273, 277].

Role of Group II mGlu Receptors in the Physiology of Stress

Group II mGlu subtypes show localization in key forebrain and limbic areas, such as the PFC, thalamus, hippocampus, and amygdala [278] and their ability to fine-tune glutamatergic neurotransmission makes these receptors attractive targets for the development of improved medication for emotional disorders. Recent studies showed that hippocampal mGlu2/3 receptor expression is reduced in the mouse OB model of depression and spontaneously depressed Flinders-sensitive line (FSL) rats [279, 280]. Moreover, recent human postmortem brain analysis demonstrated an increase in mGlu2/3 protein levels in depressed patients [281]. Particularly the mGlu2/3 activating ligands seem to be drugs with promising therapeutic potential and good safety profiles. For example, the mGlu2/3 receptor agonists such as (-)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0.]hexane-4,6 dicarboxylic acid (LY404039) and (1S,2S,5R,6S)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740) demonstrated neurochemical and behavioral effects in a very broad spectrum of models predictive of anxiolytic and anti-stress activity [58, 268, 282-286]. These mGlu2/3 receptor agonists have even progressed into phase II clinical trial, in which there was good efficacy in preventing CO_2-induced anxiety in panic attack patients [287]. Furthermore, strong preclinical evidence for potential antidepressant effects upon chronic dosing came from a study showing that 3-days of treatment with the mGlu2/3 agonist 2-amino-4-oxabicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY379268) induced a decrease of total immobility time in the FST in FSL rats [288, 289]. Interestingly, combination of the antidepressant chlorimipramine and LY379268 for 3 days substantially reduced the immobility time, supporting the hypothesis that antidepressants have a shorter latency of action if mGlu2/3 receptors are activated at the same time [280]. Especially the latter finding raises the intriguing possibility for mGlu2/3 agonists to be used as adjunctive drugs to shorten the latency of antidepressant medication, an issue that should receive strong attention, as suicide attempts are often increased particularly during the initial period of antidepressant treatment. In addition, LY379268 significantly decreased SIH responses, indicating its anti-anxiety potential [269, 290]. Interestingly, it has been shown that mGlu2, and not mGlu3, mediated the actions of LY404039 and LY379268 in mouse models predictive of antipsychotic activity [291, 292], suggesting a dominant role of the mGlu2 receptor subtype in triggering antipsychotic effects. In recent years, the number of reports about mGlu2 receptor-selective positive allosteric modulators (PAMs) has increased substantially and some of these compounds have been extensively characterized in a number of animal models [293, 294]. For instance, a recent study using the mGlu2 receptor PAM N-({4-[3-hydroxy-4-(2-methylpropanoyl)-2-(trifluoromethyl)phenoxymethyl]phenyl}methyl)-1-methyl-1H-imidazole-4-carboxamide (THIIC) showed robust activity in three assays detecting antidepressant-like activity, including the FST in mice, the differential reinforcement of low rate 72-s (DRL-72) assay and the dominant-submissive test in rats, with a maximal response similar to that of imipramine [295]. Moreover, this mGlu2 PAM showed anxiolytic-like efficacy in the SIH test in rats and the marble-burying test in mice, suggesting an important role for mGlu2 in the pathophysiology of anxiety. In addition, 1-(4-chloro-2-fluorobenzyl)-5-(4-methoxyphenyl)-2(1H)-pyridinone (ADX71149), another highly mGlu2-selective PAM, demonstrated safety and efficacy not only in phase IIa clinical testing for schizophrenia but also in anxious depression [296, 297]. The mGlu2 PAMs 2,2,2-trifluoro-N-[4-(2-methoxyphenoxy)phenyl]-N-(pyridin-3-ylmethyl) ethanesulfonamide (LY487379) and 4-[3-[(2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydroinden-5-yl)oxymethyl]phenyl] benzoic acid (biphenylindanone A, BINA) also exhibited anxiolytic effects when assessed in rodent models of anxiety such as SIH and EPM tests [290, 298].

Interestingly, and in some way paradoxically, there are also studies demonstrating antidepressant-like and anxiolytic

efficacies of mGlu2/3 receptor antagonists. Early findings were obtained in the FST in rats and TST in mice after acute administration of (1R,2R,3R,5R,6R)-2-amino-3-[(3,4-dichlorophenyl)methoxy]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039) and (1S,2S)-2-[(2S)-2-amino-3-(2,6-dioxo-3H-purin-9-yl)-1-hydroxy-1-oxopropan-2-yl]cyclopropane-1-carboxylic acid (LY341495) [299]. Importantly, several studies revealed that repeated administration of the mGlu2/3 receptor antagonist MGS0039 exhibited remarkable antidepressant-like efficacy. In this context, Palucha-Poniewiera *et al.* [300] could show that repeated administration of MGS0039 attenuated deficits in the OB model of depression in rats. Furthermore, treatment with MGS0039 for 7 days elicited a significant reduction in escape failures in the LH paradigm [301]. Additionally, MGS0039's antidepressant-like potential was demonstrated by reversing the increase of immobility in the FST induced by chronic social isolation-reared mice [302] and by reducing the increase of immobility in the FST after chronic corticosterone treatment [303]. Moreover, this mGlu2/3 receptor antagonist significantly attenuated freezing behavior in a conditioned fear stress (CFS) model [301], dose-dependently reduced SIH [304] and inhibited marble-burying behavior [305], indicating also strong anxiolytic-like potential. It was further demonstrated that systemic blockade of mGlu2/3 with LY341495 prevented stress-induced autonomic hyperactivity [304] and reduced immobility in the mouse FST and in the TST of a line of Helpless (H) mice [300, 303, 306, 307], a putative model for depression symptoms. A more recent study demonstrated that a single administration of LY341495 produced a rapid and long-lasting reversal of decreased sucrose preference caused by CUS in rats [308]. In addition, the recently developed mGlu2/3-selective NAM 4-[3-(2,6-dimethylpyridin-4-yl)phenyl]-7-methyl-8-(trifluoromethyl)-1,3-dihydro-1,5-benzodiazepin-2-one (RO4491533) also showed strong antidepressant-like efficacy in mouse FST and TST models [307], underpinning the anti-stress potential of mGlu2/3 receptor antagonists – at least in some relevant experimental animal models.

As clearly demonstrated by the recent advances above, mGlu2/3 receptors are critically involved in stress physiology and their modulation holds promise for the treatment of mood disorders such as depression and anxiety [309], and several pharmaceutical companies are interested in advancing mGlu2- and/or mGlu3 modulators (positive and negative) from discovery research into clinical development.

Role of Group III mGlu Receptors in the Physiology of Stress

Group III mGlu receptors have received somewhat less attention than those of group I or group II, mostly due to the obvious paucity of pharmacological tools available to study them [51, 55, 61, 310]. Nevertheless, they are thought to be involved in a number of disease states and physiological conditions, consistent with their role in the regulation of both glutamatergic and GABAergic neurotransmission throughout the brain [311-317]. Much of our current knowledge still relies on studies performed by direct central application of compounds and on the characterization of genetically manipulated animals under basal and under stress conditions. For instance, Tatarczynska *et al.* [318] found out that intraventricular injection of the group III mGlu receptor agonist (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I) produced both anxiolytic- and antidepressant-like effects. Its anxiolytic action was shown in both the SIH and EPM tests in mice, and in the Vogel conflict test in rats. Its antidepressant-like action was evaluated in the FST [318, 319]. Interestingly, another study showed that the antidepressant-like effects of centrally applied ACPT-I could be reversed by the group III mGlu receptor antagonist 2-amino-2-cyclopropyl-2-(4-phosphonophenyl)acetic acid (CPPG) [320]. However, these compounds are not subtype-selective, as they act at all members of group III receptors, making it impossible to allocate these effects to a specific receptor subtype. Addressing the influence of mGlu4, Klak *et al.* [321] could show that the combined administration of the mGlu4-selective PAM 7-hydroxyimino-N-phenyl-1,7a-dihydrocyclopropa[b]chromene-1a-carboxamide (PHCCC) and a non-effective dose of ACPT-1 produced antidepressant-like efficacy in the rat FST. A further study demonstrated that administration of PHCCC into the basolateral amygdala resulted in dose-dependent anti-conflict effects in the rat Vogel conflict test, indicating that positive allosteric modulation of mGlu4 receptors may be a useful therapeutic approach for anxiety [322]. More recently, the peripheral use of (1R,2S)-2-[(3,5-dichlorophenyl)carbamoyl]cyclohexane-1-carboxylic acid (VU0155041), an mGlu4 PAM [323], demonstrated anxiolytic action in the elevated zero maze [324]. In addition, the novel mGlu4 PAMs (1S,2R)-2-[(aminooxy)methyl]-N-(3,4-dichlorophenyl)cyclohexane-1-carboxamide (Lu AF21934) and 4-methyl-N-[5-methyl-4-(1H-pyrazol-4-yl)-1,3-thiazol-2-yl]pyrimidin-2-amine (ADX88178) have been reported to also induce an anxiolytic-like affect in acute rodent models including SIH, four-plate and marble-burying test, in addition to being active in multiple models of Parkinson's disease [325, 326]. Interestingly, mGlu4-deficient mice exerted increased measures of anxiety in acute models, including the open field and elevated zero maze, and impaired sensorimotor function on the rotarod test [327]. Consistent with this, they also showed enhanced amygdala-dependent cued-fear conditioning [328]. Similar to these findings, mice lacking mGlu8 showed higher measures of anxiety as compared to control animals [329, 330] and when exposed to novel, aversive environments, they exhibit greater neuronal activation in stress-related brain regions [331]. These studies suggest enhanced reactivity to stressors in mice deficient for mGlu4 or mGlu8. To go on with mGlu8, acute pharmacological stimulation with its agonist 4-[(1S)-1-amino-2-hydroxy-2-oxoethyl]phthalic acid (DCPG) reduced innate anxiety in the open field and EPM tests [332] and reduced the expression of contextual fear without affecting the acquisition and expression of cued fear [333]. Furthermore, 2-amino-2-(4-phosphonophenyl)acetic acid (RS-PPG), an mGlu8 receptor-preferring agonist, induced dose-dependent antidepressant-like effects in the FST after central administration [320]. Moreover, the mGlu8-selective PAM 2-[(4-bromophenyl)methyl-sulfanyl]-N-(4-butan-2-ylphenyl)acetamide (AZ12216052) reduced measures of anxiety in the open field and EPM tests [332].

Table 1. A summary of mGlu receptor pharmacology focusing on the selection of animal models of acute and chronic stress as detailed in this manuscript (see above).

Drug	Action	Animal Model(s)	Effect(s)	Reference(s)
Fenobam	mGlu5 NAM	SIH	anxiolytic	Porter *et al.*, 2005 [236]
MPEP	mGlu5 NAM	SIH, EPM, FST, TST, LH	anxiolytic, antidepressant-like	Spooren *et al.*, 2000 [237]; Nordquist *et al.*, 2007 [242]; Garparini *et al.*, 2008 [240]; Liu *et al.*, 2012 [241]
MTEP	mGlu5 NAM	SIH, EPM, FST, TST	anxiolytic, antidepressant-like	Klodzinska *et al.*, 2004 [247]; Palucha *et al.*, 2005 [252]; Molina-Herandez *et al.*, 2006 [248]; Pomierny-Chamioło *et al.*, 2010 [249]; Ticha *et al.*, 2011 [250]; Palucha-Poniewiera *et al.*, 2014 [356]
GRN-529	mGlu5 NAM	SIH, FST, TST	anxiolytic, antidepressant-like	Hughes *et al.*, 2013 [254]
AFQ056/ mavoglurant	mGlu5 NAM	SIH	anxiolytic	Vranesic *et al.*, 2014 [255]
Basimglurant	mGlu5 NAM	SIH	anxiolytic	Jaeschke *et al.*, 2015 [231]; Lindemann *et al.*, 2015 [233]
CTEP	mGlu5 NAM	SIH, CSDS	anxiolytic, antidepressant-like: reversal of CSDS-induced reduction of locomotion and anhedonia	Lindemann *et al.*, 2011 [228]; Wagner *et al.*, 2014 [163]
LY354740	mGlu2/3 agonist	SIH, EPM	anxiolytic	Linden *et al.*, 2004 [283]; Rorick-Kehn *et al.*, 2005, 2006 [268, 285]
LY379268	mGlu2/3 agonist	SIH, FST	anxiolytic, antidepressant-like	Matrisciano *et al.*, 2007 [288]; Satow *et al.*, 2008 [269]; Wieronska *et al.*, 2012 [290]
THIIC	mGlu2 PAM	SIH, FST	anxiolytic, antidepressant-like	Fell *et al.*, 2011 [295]
LY487379	mGlu2 PAM	SIH	anxiolytic	Wieronska *et al.*, 2012 [290]
BINA	mGlu2 PAM	SIH, EPM	anxiolytic	Galici *et al.*, 2006 [298]
MGS0039	mGlu2/3 antagonist	SIH, FST, TST, LH	anxiolytic, antidepressant-like	Chaki *et al.*, 2004 [299]; Yoshimizu *et al.*, 2006 [301]; Iijima *et al.*, 2007 [304]; Palucha-Poniewiera *et al.*, 2010 [300]; Ago *et al.*, 2013 [357]
LY341495	mGlu2/3 preferring antagonist	SIH, FST, TST, CMS	anxiolytic, antidepressant-like: reversal of CMS-induced anhedonia	Chaki *et al.*, 2004 [299]; Iijima *et al.*, 2007 [304]; Bespalov *et al.*, 2008 [306]; Ago *et al.*, 2013 [357]; Dwyer *et al.*, 2013 [308]
RO4491533	mGlu2/3 NAM	FST, TST	antidepressant-like	Campo *et al.*, 2011 [307]
ACPT-I	mGlu4/6/7/8 agonist	SIH, EPM, FST	anxiolytic, antidepressant-like	Tatarczynska *et al.*, 2002 [318]; Stachowicz *et al.*, 2009 [319]
PHCCC	mGlu4 PAM	FST	antidepressant-like (in combination with ACPT-I)	Klak *et al.*, 2007 [321]
Lu AF21934	mGlu4 PAM	SIH	anxiolytic	Slawinska *et al.*, 2013 [325]
ADX88178	mGlu4 PAM	EPM, FST	anxiolytic, antidepressant-like	Kalinichev *et al.*, 2014 [326]
DCPG	mGlu8 agonist	EPM	anxiolytic	Duvoisin *et al.*, 2010 [332]
AMN082	mGlu7 agonist	SIH, EPM, FST, TST	anxiolytic, antidepressant-like	Palucha *et al.*, 2007 [341]; Stachowicz *et al.*, 2008 [345]; Palazzo *et al.*, 2008 [346]; Bradley *et al.*, 2012 [344]; O'Connor and Cryan, 2013 [351]; Palucha-Poniewiera *et al.*, 2010, 2013, 2014 [72, 342, 343]
ADX71743	mGlu7 NAM	EPM	anxiolytic	Kalinichev *et al.*, 2013 [350]
XAP044	mGlu7 antagonist	SIH, EPM, TST	anxiolytic, antidepressant-like	Gee *et al.*, 2014 [353]

Abbreviations: NAM, negative allosteric modulator; PAM, positive allosteric modulator; EPM, elevated plus maze; SIH, stress-induced hyperthermia; FST, forced swim test; TST, tail suspension test; LH, learned helplessness; CMS, chronic mild stress; CSDS, chronic social defeat stress.

However, as this anxiolytic effect was still present in mGlu8-KO mice, the effect of 2-{[(4-bromophenyl)methyl] sulfanyl}-N-[4-(butan-2-yl)phenyl]acetamide (AZ12216052) on measures of anxiety likely involves molecular targets other than mGlu8, too [324]. Nevertheless, the behavioral data so far suggest that mGlu4 and mGlu8 receptor activation may render anxiolytic, anti-stress as well as antidepressant-like effects [334].

With respect to mGlu7, there is clear evidence for a role of this receptor in fear and stress physiology from studies using mGlu7-KO mice [333, 335, 336]. Ablation of mGlu7 in mice was shown to result in reduced amygdala-dependent conditioned fear and aversion. The phenotype of reduced anxiety- and stress-related behaviors and physiology of mGlu7-deficient mice extends also to tests for innate anxiety and despair [335, 336]. In addition, these mice also show an upregulated glucocorticoid receptor-dependent feedback suppression of the HPA axis [209], further supporting mGlu7's critical role in stress physiology. Mitsukawa *et al.* [337] characterized an mGlu7-selective agonist, namely N,N'-bis[di(phenyl)methyl]ethane-1,2-diamine (AMN082), as a compound which is orally active and penetrates the blood-brain barrier, that enabled to further study mGlu7's potential role in stress physiology. In the fear-potentiated startle paradigm, a model of acute stress, AMN082 impaired acquisition but enhanced extinction of conditioned fear, while mGlu7 knockdown using short interfering RNA attenuated extinction [338, 339]. In another study, Dobi *et al.* [340] demonstrated that direct AMN082-injection into the basolateral complex of the amygdala also facilitated extinction of contextual fear. Together, these data support a clear role for mGlu7 in both acquisition and extinction of conditioned fear. Moreover, AMN082 elevated plasma levels of the stress hormones ACTH and CORT [337], induced antidepressant-like effects in the FST and TST [72, 341-344], and demonstrated robust anxiolytic efficacy in the SIH response, four-plate- and EPM test [345, 346]. At a first glance, these effects seem to be in contradiction with the anxiolytic- and antidepressant-like behavioral changes observed in mice lacking mGlu7 or after siRNA-mediated knockdown of the receptor [347]. However, AMN082 has been shown also to induce a rapid and lasting internalization of mGlu7 protein, which could well translate into functional antagonism of the receptor [348]. A further explanation for AMN082's antidepressant-like profile in rodents would be that AMN082 not only binds to mGlu7 but with weaker affinity also to monoamine transporters, similar to its primary metabolite, *N*-benzhydrylethane-1,2-diamine (Met-1), which inhibits serotonin and norepinephrine reuptake transporters with a physiologically relevant affinity [349].

Two systemically active mGlu7 NAMs have yielded divergent results in behavioral tests despite displaying very similar pharmacological properties *in vitro*. 6-(2,4-dimethylphenyl)-2-ethyl-4,5,6,7-tetrahydro-1,3-benzoxazol-4-one (ADX71743) was shown to have robust anxiolytic effects in the EPM and the marble burying test [350]. In contrast, 6-(4-methoxyphenyl)-5-methyl-3-(pyridin-4-yl)-4H,5H-[1,2]oxazolo[4,5-c]pyridin-4-one (MMPIP) was reported to have little anxiolytic activity but reversed antidepressant-like effects of AMN082 in rats [343, 351]. In addition, various behavioral studies also revealed that MMPIP impaired cognitive performances in the object recognition and the object location test [352]. As opposed to *e.g.* MMPIP, the recently discovered and first mGlu7-selective orthosteric antagonist 7-hydroxy-3-(4-iodophenoxy)-4H-chromen-4-one (XAP044) was shown to display binding within the VFTD of mGlu7 and a quite broad mode of functional mGlu7-blockade across multiple *in vitro* tests [353]. XAP044 is systemically active and demonstrates a wide spectrum of anti-stress-, antidepressant-, and anxiolytic-like efficacy *in vivo* [353]. This supports the view that pharmacological blockade of mGlu7 *in vivo* might be a viable path forward attempting to reverse stress-related pathophysiological states in psychiatric illness. In line with this, human genetic studies with depressed siblings and recurrent MDD patients pointed at GRM7 (the gene coding for mGlu7 receptors) as a gene potentially involved in human depression [354, 355]. Taken together, considerable progress has been made in recent years in increasing our understanding of group III mGlu receptors within the CNS, and has remarkably revealed key roles for these receptors in acute stress, fear- and depression-related behavior, thereby emphasizing the therapeutic potential of group III-directed ligands and asking for future studies under chronic stress conditions (see below).

CONCLUSION AND OUTLOOK

Encouraging evidence has emerged from both preclinical and clinical research in recent years, supporting key roles for the brain glutamatergic neurotransmitter system in the physiology of psychiatric disorders. However, only little is known about the contribution of the glutamate system to the pathophysiology following chronic psychosocial stress, which is the most acknowledged risk factor for emotion disorders, such as anxiety and depression [1, 2, 4-7, 9]. Moreover, current drug discovery efforts targeting the mGlu receptors led to the identification of pharmacological tools with promising efficacy in psychiatric conditions [51, 55, 58, 65, 71, 231, 233, 358]. The potential of these pharmacological tools in the manifestation of physiological and behavioral consequences of chronic psychosocial stress still needs to be investigated. On a preclinical basis, the CSC paradigm might be an appropriate animal model, as it utilizes chronic psychosocial stressor exposure and results in decreased GC signaling and concomitant somatic, immunological, and affective pathologies, such as an overall proinflammatory- and cancer-prone phenotype and an anxiogenic and substance abuse phenotype [40, 41, 140, 179, 180, 186, 196, 359]. All these consequences are relevant for the development of somatic, *e.g.* gastrointestinal, and/or psychiatric disorders and the question whether mGlu receptors have the potential to exert control on these consequences is of great interest. Early evidence for the potential involvement of mGlu receptor subtypes in chronic psychosocial stress pathology comes from recent studies described above, suggesting that the mGlu7 receptor might play a controlling role in the PFC and the mGlu5 receptor in the hypothalamus. The recent development of CTEP and basimglurant, two compounds with markedly improved pharmacokinetic and safety profiles as compared to previous mGlu5 NAMs, such as MPEP and MTEP, may be most suitable to study the long-term effects

of mGlu5-blockade *in vivo* following chronic stress exposure. Most notably, CTEP's sufficiently long half-life amenable for once daily administration in rodents and its high *in vivo* potency to achieve a low application dose makes it a suitable compound for chronic application and for the study of mGlu5's role in chronic stress conditions. Indeed, first evidence of efficacy already comes from a very recent study conducted by Wagner *et al.* [163], who demonstrated that sustained mGlu5 receptor blockade *via* chronic administration of CTEP was able to recover CSDS-induced behavioral alterations [163]. The finding, that CTEP did not reverse the stress-induced physiological changes, requires further investigation. A potentially profitable approach in this regard may be to investigate whether chronic CTEP administration can attenuate the various physiological, immunological, and also behavioral consequences of chronic psychosocial stress induced by CSC exposure. Such studies may suggest future application routes for mGlu5 NAMs in chronic clinical conditions, including somatoform psychiatric disorders.

The mGlu7 receptor is also a promising target in chronic stress physiology, but the question still remains, which mechanism of action – its activation or blockade – might be effective in ameliorating the detrimental consequences of chronic psychosocial stress. Considerable progress has been made with the discovery of the mGlu7 agonist AMN082 [337] and the mGlu7 NAM ADX71743 [350], two compounds that have already shown robust efficacy in animal models for anxiety and depression, but have not yet been investigated in any context of chronic or even psychosocial stress. For the present time, it is very difficult to speculate whether activation or inhibition of the mGlu7 receptor would be more efficacious in reversing the consequences of chronic stress in man. However, the characterization of the recently discovered orthosteric-like mGlu7 antagonist XAP044 [353], which shows wide spectrum anti-stress (acute), antidepressant-, and anxiolytic-like efficacy *in vivo*, might provide an additional and suitable tool compound to elucidate the role of mGlu7 under chronic psychosocial stress conditions, at least in rodents. Taken together, there is emerging evidence that makes it worthwhile to further investigate in detail the potentially beneficial roles of especially mGlu5 and mGlu7 subtype-selective modulation in the context of chronic psychosocial stress and to provide a better understanding of the neural mechanisms involved and regulated by mGlu receptors. Besides providing fundamental neurophysiological insights, these investigations will hopefully stimulate drug development towards mGlu5- and mGlu7-targeted therapies aiming at the large panel of human chronic stress-induced neuropsychiatric disorders.

CONFLICT OF INTEREST

All three authors who contributed to this manuscript state that they have no conflict of interest with this work.

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