The potential risk of chronic stress

and

the NMDA- and Glucocorticoid receptor as possible targets for innovative antidepressants

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Layman´s summary

Stress is a normal reaction of the body to threats. In low levels it can help you perform under pressure but when stress persists, this can have negative effects. Stress hormones like cortisol and glutamate can affect the brain and cause brain damage. This brain damage can eventually lead to mental disorders like depression, anxiety and posttraumatic stress disorder (PTSD). Medication is available for these disorders, but for PTSD, medication is limited. Therefore, this thesis proposes suggestions for future therapy for PTSD patients, not only to treat the symptoms but maybe even prevent brain damage.

Abstract

Stress leads to elevated levels of adrenalin and cortisol. This is a natural response of the brain and body, called “fight-or-flight”response. Adrenalin and cortisol bind to the adrenergic or glucocorticoid receptors and via their signaling pathway, this leads to vasoconstriction, increased heart rate, bronchodilation etcetera, preparing the body to fight or flight. But when the stress persists, and the cortisol and adrenalin levels are elevated for a prolonged time, this could lead to brain damage like neurotoxicity and eventually even to stress-related disorders as anxiety disorders or depression. This review describes the stress-response of the body and the risks of chronic stress. Stress-related disorders and the available treatments were summarized and clarified, in order to understand the mechanism of action and to explain why these treatments are sometimes not sufficient enough. For Posttraumatic Stress Disorder (PTSD), limited medication is available. Therefore, additional literature research was performed on PTSD. The results of human and animal studies were summarized to get insight in the pathophysiology of PTSD and the differences in several brain regions. It seemed that the prolonged elevated levels of corticosteroids could cause permanent brain damage. The available medication is able to reduce the depression or anxiety by treating the symptoms, but these drugs are not able to prevent or restore the brain damage. Therefore, innovative targets for psychotropic drugs are needed and were proposed in this review, namely the glucocorticoid receptor (GR) and the NMDA receptor (NMDAR). These receptors were chosen as new targets for PTSD medication, since corticosteroids and glutamate cause brain damage. Literature describing experiments with (partial) antagonists for these receptors in schizophrenic and OCD patients showed to be effective. It may be clear that chronic stress could lead to permanent brain damage and that the GR and NMDAR could be important targets in PTSD. Medication based on antagonizing the actions of these receptors could lead to reduction of brain damage in PTSD and possibly even to recovery, in contrast to the available, symptomatic treatment for PTSD.

Chapter 1: Stress, chronic stress and potential risks

Stress is a normal response of the body to potential risks. But when stress persists, and levels of stress-related neurotransmitters as adrenalin or cortisol are elevated for a prolonged time, brain damage and even stress-related disorders could be developed. Medication for stress-related disorders like anxiety disorders, depression or posttraumatic stress disorder (PTSD) are already available but are not always sufficient; innovative drugs are desired. In order to find an innovative target for stress-related disorders, first the stress response must be well understood. This chapter describes the quick and slow stress response, which hormones or neurotransmitters are involved and the effect of the response on several brain regions. After that, an overview of the stress-related disorders and the available drugs is given. This overview shows which receptors or transporters are already used as a target and which could be innovative. In chapter 3, the glucocorticoid receptor (GR) and the NMDA receptor (NMDAR) and the mechanism of action of these two receptors involved in the stress response were described to investigate whether these receptors could be interesting targets. Finally, two innovative targets were chosen and explained in chapter 4. Together, this review will lead to more insight in the effect of chronic stress and the disorders related to it, how these disorders are treated at this moment and suggestions are made for two innovative targets.

Potential risks or threats are called stressors, and could cause responses via the activation of the autonomic nervous system and the hypothalamopituitary-adrenal (HPA) axis. Respiratory distress or pain caused by stressors are registered in the brainstem and activates an immediate response of the sympathetic nervous system. Adrenaline and noradrenaline are released from the adrenal medulla while the parasympathetic nervous symstem releases acetylcholine to prevent overshooting of the stress-reaction. This response of the sympathetic nervous system is called “quick stress response”, since registration of potential threats leads to immediate release of adrenaline and noradrenaline [Joels et al. 2012]. These neurotransmitters bind to adrenergic receptors in the body and this causes several effects; for example vasoconstriction, tachycardia and bronchidilatation, so that the body is prepared to fight or flight [Rang & Dale, 2007, p.168].

In most cases though, additional brain regions are activated by the stressors, leading to activation of a “slow stress response”. In this response, stressors activate the HPA axis, where neurons in the paraventricular nucleus (PVN) of the hypothalamus produce corticotrophin-releasing hormone (CRH) and vasopressin. These hormones reach the anterior pituitary, leading to secretion of adrenocorticotrophin hormone (ACTH) [Gillies et al. 1982]. Secretion of ACTH leads to activation of the adrenal cortex, where corticosteroids are produced and released; cortisol in humans and corticosterone in rodents. Together, these actions represent the HPA axis (Figure 1). During stress, corticosteroids can control the intensity and duration of the stress response via negative feedback loops on the hypothalamus and anterior pituitary. Both stress systems, quick and slow stress response, work together to restore homeostasis [Joels et al. 2012].

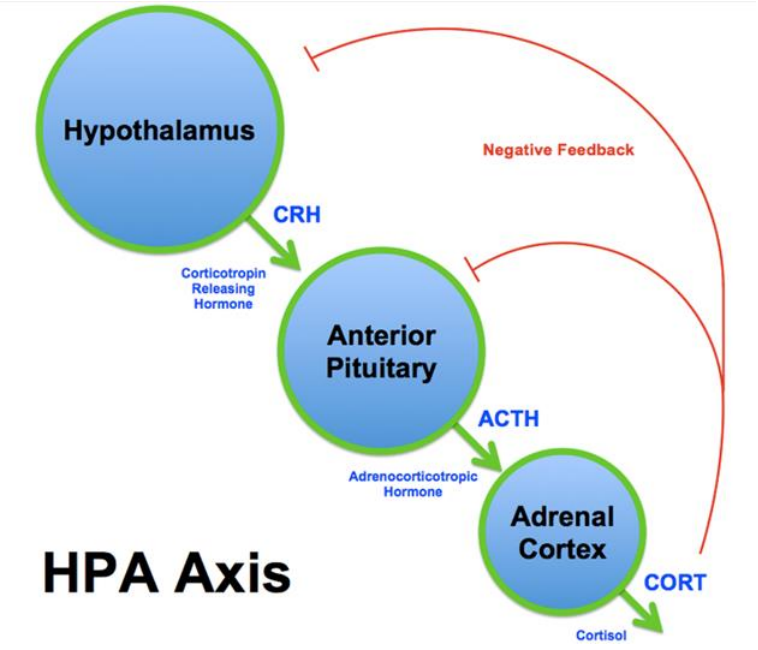


Figure 1, schematic overview of the HPA axis, CRH and vasopressin are produced by the hypothalamus. CRH reaches the anterior pituitary, which releases ACTH. ACTH activates the adrenal cortex leading to production and release of corticosteroids. Cortisol controls intensity and duration of the response via negative feedback on the hypothalamus and anterior pituitary.

The hippocampus expresses high levels of adrenergic receptors and is important for learning and memory. The amygdala is associated with physiological and behavioral fear responses and the prefrontal cortex (PFC) has an important role in extinction of learning and in working memory. All three brain regions, the hippocampus, amygdala and PFC (figure 2), are affected by stress hormones [McEwen, 2004]. Animal studies were performed where all three regions responded to repeated stress; the neurons in the amygdala showed a growth response while neurons in the PFC and the hippocampus showed atrophy [McEwen, 2004]. These effects of corticosteroids during chronic stress could lead to psychiatric disorders like depression, anxiety disorders or even posttraumatic stress disorder (PTSD).

According to Nugent et al., the hippocampus has a major role in the stress response, beside its role in learning and memory. Several receptors are highly expressed in the hippocampus, among which the glucocorticoid receptor (GR) and the N-methyl-D-aspartate receptor (NDMAR). Both receptors are involved in the stress response and could therefore be interesting targets for novel treatments for stress-related disorders.

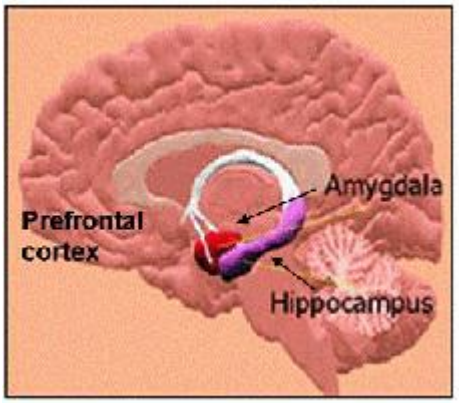


Figure 2, the hippocampus, amygdala and prefrontal cortex (PFC) are affected by stress hormones; neural growth was found in the amygdala while neurons in the PFC and the hippocampus showed atrophy.

This chapter described the quick and slow stress responses and the involved brain regions, namely the PFC, the hippocampus and the amygdala. Research in animals showed that chronic stress could lead to psychiatric disorders. The next chapter gives an overview of psychiatric stress-related disorders and the available medication. This overview was made in order to get insight in their mechanism of action and to find an innovative target for stress-related disorders.

Chapter 2: Drugs available for stress disorders

Now that the stress responses, involved brain regions and the effect of chronic stress on the brain were described, an overview was made of the available drugs for stress disorders. This chapter will define the different groups of psychotropic drugs and their mechanism of action, to get an insight in the targets already chosen and possible innovative targets for psychotropic drugs.

Psychotropic drugs are drugs that alter neurotransmitter levels in the brain by acting on the CNS, resulting in changes in mood and behavior, and they target one of the transporters for a neurotransmitter, G-coupled receptors or ligand-gated ion channels. SERT is a transporter, it transports serotonin from the synaptic gap back into the presynaptic neuron. Other neurotransmitter transporters can also serve as targets for psychotropic drugs. The neuroactive drugs can be divided in several groups .The first group consists of antidepressant drugs, suppressing the symptoms of a depression. This group includes Monoamine oxidase (MAO) inhibitors, tricyclic antidepressants (TCA's) and selective serotonin reuptake inhibitors (SSRI's). The second group, anxiolytics and sedatives, reduce anxiety and cause sleep. Examples of this group are barbiturates and benziodiazepines. The third group is the antipsychotic drugs, these drugs reduce the symptoms of schizophrenic patients. Think of clozapine, chlorpromazine, haloperidol [Rang & Dale, 2007, page 477].

Antidepressants can be divided in several groups, based on their mechanism of action (Figure 3). There are non-selective uptake inhibitors called tricyclic antidepressants (TCA's), selective reuptake inhibitors (SSRI's and SNRI's) and MAO inhibitors [van Loenen, 2008, p.96].

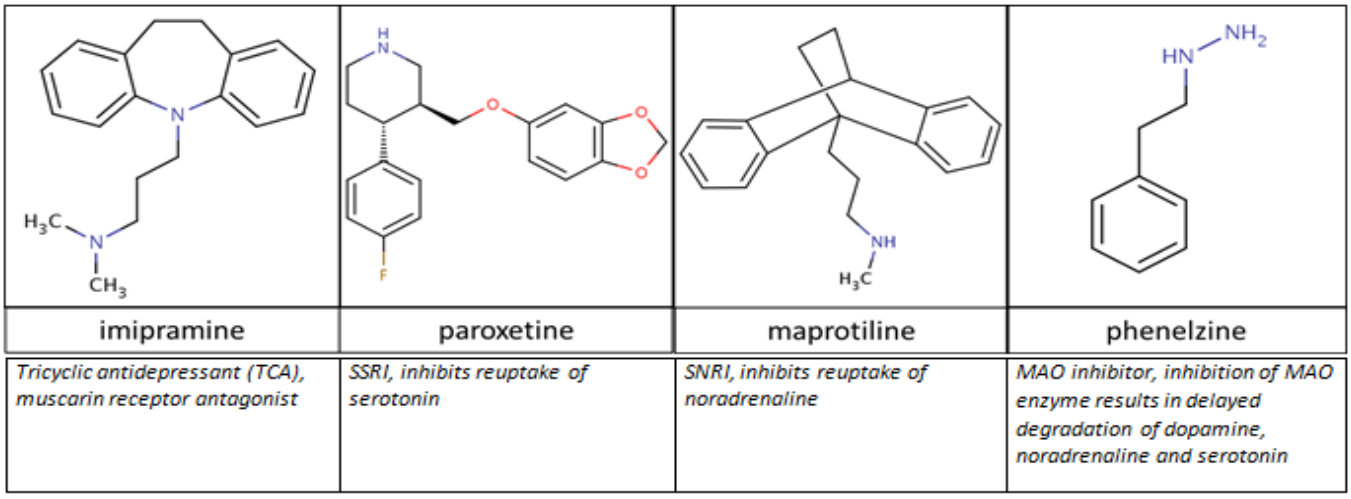


Figure 3, chemical structures and mechanism of action of imipramine, paroxetine, maprotiline and phenelzine, widely used antidepressants.

TCA's act on the parasympathicolytic nerve system. By blocking the muscarin receptor, the release of noradrenalin is inhibited, leading to reduction of anxiety or depression. Side effects of these drugs are dizziness, obstipation, tachycardia, sweatening and hypotension [Rang & Dale, 2007, p.562-563; van Loenen, 2008, p.113].

SSRI's inhibit the reuptake of serotonin, resulting in more serotonin available in the synaptic gap. This induced serotonin availability improves the symptoms and mental wellbeing of a patient. Side effects of SSRI's, due to the induced serotonin levels, are gastrointestinal disturbances, diarrhea, obstipation, headache, insomnia, and sweating [Rang & Dale, 2007, p.566-567; van Loenen, 2008, p.117].

SNRI's are comparable with SSRI's, only these drugs induce the noradrenalin levels instead of serotonin levels in the synaptic gap by blocking its reuptake. Side effects of SNRI's are nausea, diarrhea, insomnia, sedation, headache and dizziness [van Loenen, 2008, p.114].

MAO inhibitors inhibit MAO-enzyme, resulting in delayed degradation of dopamine, noradrenaline and serotonin. Side effects are nausea, hypertension and sleep complaints [van Loenen, 2008, p.116].

SSRI's could also be prescribed for anxiety disorders, since higher serotonin availability leads to decrease of symptoms of anxiety. Next to SSRI's, benzodiazepines, buspirone or β-adrenoceptor antagonists as propanolol are used in anxiety disorders (Figure 4). Binding of benzodiazepines to $GABA_A$ receptor leads to Cl^- influx, which inhibits firing of new action potentials. This also explains the side effects as dizziness, nausea, headache, sedation and loss of coördination [van Loenen, 2008, p.66]. Buspirone, a selective 5-HT_{1A} agonist, could also be used in anxiety disorders. Binding to the receptor leads to an induction of serotonin. Buspirone could give side effects comparable to benzodiazepines, but without sedation and loss of coordination [van Loenen, 2008, p.69]. Propanolol inhibits symptoms of anxiety (tremor, tachycardia, sweatening) by blocking the β-adrenergic receptor. Side effects are for example bradycardia or hypotension [van Loenen, 2008, p.300-301].

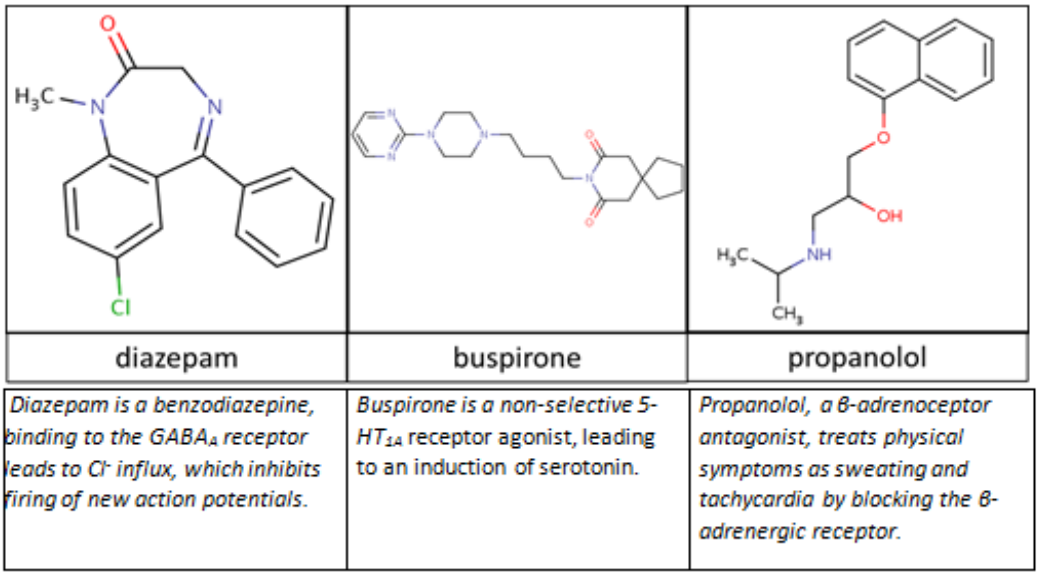


Figure 4, chemical structures and mechanism of action of diazepam, buspirone and propanolol; widely used anxiolytics

An overview of the stress-related disorders and the available drugs is given in table 1. For PTSD, SSRI's or TCA's are prescribed but only as supportive drugs next to psychological treatment [FDA website; van Loenen, 2008, p.60]. Therefore, additional medication was desired for PTSD patients. In order to find innovative targets, more literature research was done on PTSD. Human studies were found showing differences in activity or volume of different brain regions in PTSD patients compared to healthy volunteers. Next to that, animal studies were performed by different research groups, showing neural changes (for example changes in neurotransmitter concentrations) in several brain regions. The results of these studies are summarized, and could contribute to determination of an innovative target for PTSD medication.

Stress-related disorder	Available drugs	Examples	Mechanism of action	Side effects
Depression	Tricyclic antidepressants (TCA's)	Venlafaxine, amitriptyline, imipramine	Muscarin receptor antagonists	Dizziness, obstipation, tachycardia, sweatening, hypotension
	Selective serotonin reuptake inhibitors (SSRI's)	Fluoxetine, fluvoxamine, paroxetine, sertraline	Serotonin reuptake in synaptic gap inhibited, resulting in improved availability of serotonin in synaptic gap	Gastrointestinal disturbances, nausea, diarrhea, obstipation, headache, insomnia, bleedngs, sweating
	Seective noradrenaline reuptake inhibitos (SNRI's)	Maprotiline, venlafaxine, duloxetine	Noradrenaline reuptake inhibited, resulting in improved availability of noradrenaline in synaptic gap	Nausea, diarrhea, insomnia, sedation, headache, dizziness
	Monoamine oxidase (MAO) inhibitors	Phenelzine, tranylcypromine, moclobemide	Inhibit MAO-enzyme, resulting in delayed degradation of dopamine, noradrenaline and serotonin	Nausea, hypertension, sleep complaints
Anxiety Disorders	Selective serotonin reuptake inhibitors (SSRI's)	Fluoxetine, fluvoxamine, paroxetine, sertraline	Serotonin reuptake in synaptic gap inhibited, resulting in improved availability of serotonin in synaptic gap	Gastrointestinal disturbances, nausea, diarrhea, obstipation, headache, insomnia, bleedngs, sweating
	benzodiazepines	Diazepam, clonazepam, triazolam, lorazepam etc.	Binding to $GABA_A$ receptor leads to enhancement of response	Dizziness, nausea, headache, sedation and loss of coördination
	Buspirone	Buspirone	Non-selective 5-HT_{1A} receptor agonist	Dizziness, nausea, headache
	B-adrenoceptor antagonists	Propanolol	Blocking of β-receptors leads to treatment of physical symptoms like sweating, tremor and tachycardia	Bradycardia, hypotension, dizziness, heart failure, gastrointestinal disturbances, exhaustion, headache
Post-traumatic stress disorder	Selective serotonin reuptake inhibitors (SSRI's)	Paroxetine, sertraline	Serotonin reuptake inhibited, resulting in improved availability of serotonin in synaptic gap	Headache, nausea, gastrointestinal disturbances, insomnia, agitation, bleedings, sweating
	Tricyclic antidepressants (TCA's)	Imipramine	Muscarin receptor antagonists	Dizziness, obstipation, tachycardia, sweatening, hypotension

Table 1, an overview of the stress-related disorders and the available treatments

Posttraumatic Stress Disorder (PTSD)

Posttraumatic Stress Disorder (PTSD) is a psychiatric disorder and mostly affects adults who have experienced a life-threatening event or a trauma. Diagnosis of PTSD is done according to DSM-5 Diagnostic and Statistical Manual of Mental Disorders [http://www.psychiatry.org/practice/dsm/dsm5]: "The diagnostic criteria identify the trigger to PTSD as exposure to actual or threatened death, serious injury or sexual violation. The exposure must result from one or more of the following scenarios, in which the individual:

- Directly experiences the traumatic event
- Witnesses the traumatic event in person
- Learns that the traumatic event occured to a close family member or close friend
- Experiences first-hand repeated or extreme exposure to aversive details of the traumatic event

The individual can show avoidance of trauma-related stimuli, re-experience the trauma and negative alterations in cognitions and mood."

Psychological instead of pharmaceutical treatment is recommended for patients with PTSD. Therapy or anxiety management are often used as a treatment. Medication can be prescribed for support. The Food and Drug Administration(FDA) has approved two medications as a treatment for adults diagnosed with PTSD [FDA website], namely sertraline (Zoloft) and paroxetine (Paxil). Next to the drugs mentioned above, fluoxetine or some TCA's (for example amitriptyline, imipramine) could be prescribed for support [Van Loenen, 2008,p.60].

SSRI's used as antidepressant drugs also show efficacy in anxiety disorders [Rang & Dale, 2007, p.477] and could possibly be prescribed for PTSD. Other medications like benzodiazepines, antipsychotics or antidepressants could also be prescribed, but for these medications efficacy has not yet been proven.

The amygdala, hippocampus and ventromedial prefrontal cortex are involved in fear [McEwen, 2004; Sullivan et al. 2013]. These regions in the brain contain serotonin-1A receptors (5-HT_{1A}), which are particularly related to anxiety expression in both rodents and humans. Disruption of 5-HT_{1A} expression (for example caused by chronic stress) may lead to a lifelong anxious phenotype [Sullivan et al. 2013].

PTSD and also other anxiety disorders are probably caused by longterm exposure to corticosteroids and/or adrenaline. This longterm exposure could lead to permanent changes in neurogenesis and even neurotoxicity, and could therefore cause psychiatric disorders [McEwen, 2000; Radley et al., 2006; Sapolsky, 2000]. Human studies were performed to investigate the effect of longterm exposure of adrenalin and corticosteroids on activity or volume of hippocampus, hypothalamus and amygdala. Next to that, animal studies showed impaired or elevated levels of adrenalin and corticosteroids in the hippocampus, hypothalamus and amygdala. These studies can give insight in the effect of these neurotransmitters on neurogenesis and development of anxiety disorders.

Studies were published using magnetic resonance imaging (MRI) showing that patients with PTSD have a reduced hippocampal volume compared to healthy voluunteers [Bremner et al. 1995; Gurvits et al. 1996; Gilbertson et al. 2002]. Chao et al. reported an inversed relation between the right hippocampal volume and PTSD duration. This may suggest that the hippocampus is sensitive to environmental stress in PTSD. This hippocampal reduction may be due to chronic exposure to corticosteroids, excessive glutamate leading to cell atrophy or death, or inhibition of neurogenesis

[McEwen, 2000; Sapolsky, 2000; Radley et al. 2006]. According to Sullivan et al, the hippocampus showed lower 5-HT_{1A} binding potential compared to the PFC, amygdala and brainstem raphe nuclei in medication-free PTSD patients. PTSD patients showed higher 5-HT_{1A} binding potential compared to healthy volunteers. Next to that, higher binding potential was found in females compared to males.

Animal studies concerning PTSD were also performed. These studies are necessary to study neural changes as neurotransmitter concentrations and to develop innovative treatments. Animal studies showed that exposure to chronic stress can cause brain damage, particularly in the hippocampus. This was caused by increased levels of corticosteroids and excitotoxins [Sapolsky et al. 1990; McEwen and Sapolsky 1995].

Recent research indicates that abnormalities in the HPA axis, the immune system and neurotransmitter modulation in the brain may play critical roles in development of PTSD [Wilson et al. 2014]. However, it still remained unclear which neurotransmitters are up- or downregulated during PTSD progression. Therefore, Wilson et al. set up an experiment to investigate whether PTSD alters levels of neurotransmitters in the brain. For this experiment, rats were exposed to stress by the predator exposure/psychosocial stress model, to induce PTSD development. After 32 days, the rats were sacrificed and the hippocampus and prefrontal cortex (PFC) of the rats were isolated to analyze levels of several neurotransmitters (among which serotonin and norepinephrine) in these brain regions. After analysis with HPLC, researchers found upregulation of norepinephrine and downregulation of serotonin in both hippocampus and PFC (Figure 5). This indicates that serotonin and norepinephrine are modulated by chronic stress [Wilson et al. 2014].

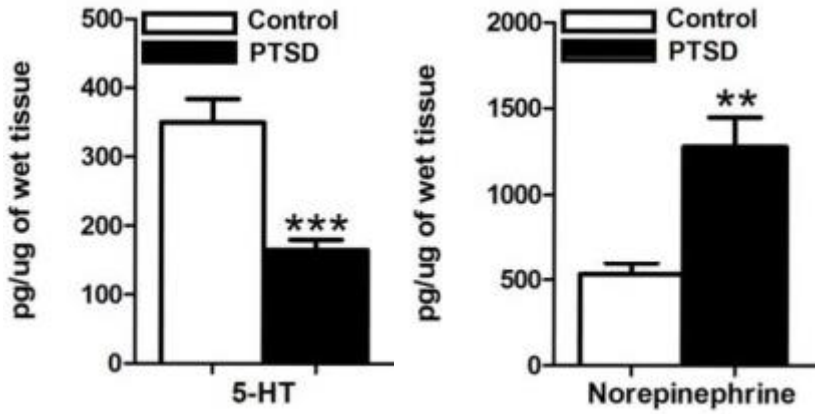


Figure 5, adapted from Wilson et al. 2014, showing significant downregulation of serotonin (5-HT) and significant upregulation of norepinephrine in the hippocampus in response to the predator exposuer/psychosocial stress model. In the PFC, serotonin and norepinephrine showed comparable results.

This chapter gave an overview of the stress-related disorders and their treatments. Posttraumatic stress disorder was highlighted in this chapter, since less medication is available for patients with this disorder. The results of several studies were summarized to get insight in changes in brain regions and neurotransmitter concentrations. Already in 1990, Sapolsky et al. concluded that increased levels of corticosteroids causes brain damage, particularly in the hippocampus. Also McEwen (2000) and Sapolsky et al. (2006) highlighted this effect of longterm exposure to corticosteroids. Therefore, the glucocorticoid receptor (GR) could be an interesting new target for PTSD medication. Also the NMDA receptor (NMDAR) could be an interesting new target, since excessive glutamate, ligand of this receptor, release also leads to neural damage [Stahl, 2008, p.301-302]. In chapter 3, both targets will be defined.

Chapter 3: The NMDA and Glucocorticoid receptors

Kim and Yoon (1998) described that the NMDAR and GR are highly expressed in the hippocampus during longterm stress exposure . Chronic stress could lead to changes in hippocampal structure and in behavior, due to excessive GR activation. Next to that, chapter 2 showed that not many drugs are available for PTSD and none of the available drugs target the GR or NMDAR. The available drugs treat PTSD symptoms as anxiety, but these drugs are not able to prevent or restore brain damage caused by elevated levels of corticosteroids or glutamate. Therefore, the GR and NMDAR could be interesting targets for innovative drugs. This chapter describes both receptors and their mechanism of action.

§2.1: The NMDA-receptor

The N-methyl-D-aspartate receptor (NMDAR) is a postsynaptic glutamate receptor linked to an ion channel. This ion channel is highly permeable for calcium, which is critical for the development of the Central Nerve System (CNS). In resting state, the calcium channel of the NMDA receptor is blocked by magnesium and can only open when three things occur on the same time (Figure 6): [Stahl, 2008, p.286]

1) Glutamate binds to its binding site on the NMDA receptor
2) Glycine or d-serine binds to its binding site on the NMDA receptor
3) Depolarization occurs, resulting in removal of the magnesium plug

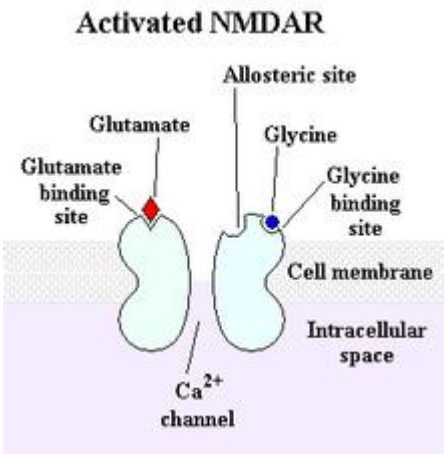


Figure 6, Glutamate and glycine bind to the NMDA receptor. When depolarization occurs at the same time, the magnesium plug will be removed (not shown), leading to Ca^{2+}-influx.

Together with the AMPA-receptor and kainate receptors, NMDAR modulates excitatory postsynaptic neurotransmission triggered by glutamate.

The resulting increase in Ca^{2+} leads to stimulation of PKC and other kinases. PKC phosphorylates several proteins in a signaling pathway. These proteins control gene transcription in postsynaptic cells. Relase of NOS facilitates glutamate release. Excessive glutamate release leads to neural damage [Stahl, 2008, p.301-302].

§2.2: the Glucocorticoid receptor

There are two types of corticosteroid receptors, namely the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR) [Reul and de Kloet, 1985]. Both receptors are found in the hippocampus among others, but for the MR the main ligand is the hormone aldosterone, while the main ligand of the GR is cortisol. Aldosterone is less prevalent than cortisol in the brain, so in the hippocampus cortisol is the main ligand of MRs. Next tot hat, cortisol binds to the MRs with a 10-fold higher affinity compared to GRs. This leads to activation of MRs with low levels of corticosteroid hormones, and (excessive) activation of GRs during peak levels of cortisol, for example during chronic stress [De Kloet et al. 2005]. This implicates that GRs are the main receptor for cortisol during chronic stress. Cortisol, released by the adrenal cortex during stress, binds to a GR in the cytoplasm of the cell. The receptor is bound to a chaperone protein called heat-shock protein 90 (HSP90). Binding of cortisol to the GR leads to dissociation of HSP90 from the receptor. The cortisol-receptor complex is then able to travel into the nuceus to stimulate transciption of glucocorticoid-responsive genes (Figure 7) [Stahl, 2008, p.172]. Overstimulation of the GR, for example during long-term exposure of cortisol, could lead to neural damage.

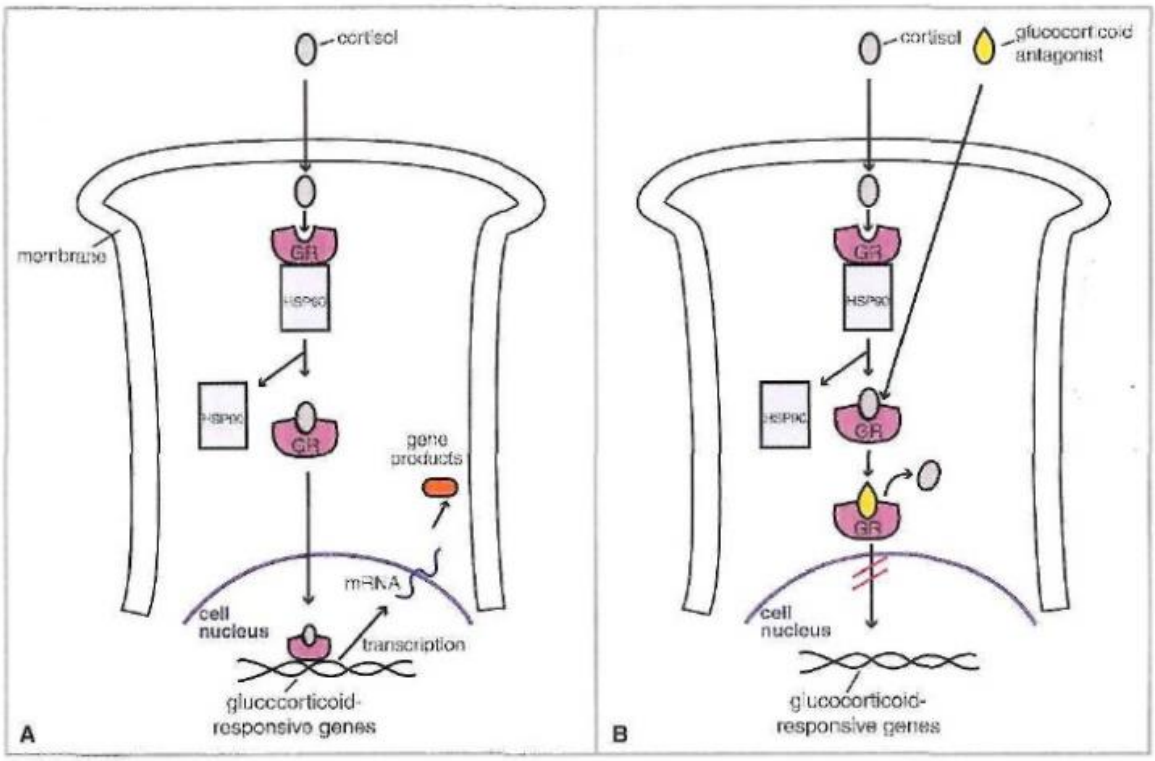


Figure 7, cortisol binds to the receptor and the complex travels into the nucleus, after HSP90 has dissociated. In the nucleus, transcription of glucocorticoidresponsive genes is stimulated by the complex.

A GR antogonist is able to prevent mRNA production of glucocorticoid-responsive genes by binding to the GR. There is a competition between cortisol and the antagonist at GR, leading to lack of expression of glucocorticoid genes. Mefipristone is an example of a GR antagonist [Yang et al. 2004; Mayer et al. 2006; Oomen et al. 2007; Hu et al. 2012; Kamal et al. 2014; Stahl, 2008, p.172].

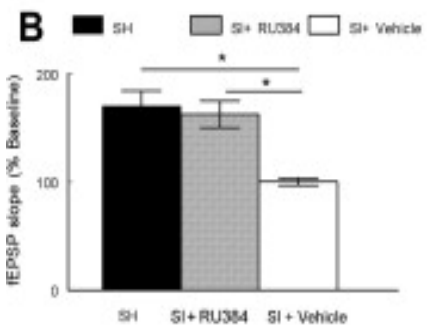
In conclusion, overactivation of both receptors, which is the case during longterm stress exposure, leads to neural damage and eventually to stress-related disorders. These receptors could be interesting targets for innovative psychotropic drugs. Chapter 4 will describe how these receptors could be used as targets for a possible new PTSD treatment.

Chapter 4: Drug Innovation; GR and NMDAR as new possible targets?

As explained above, long-term exposure to corticosteroids or glutamate could lead to stress-related disorder as depression, anxiety disorders or PTSD. In chapter 2, the medications currently available for these disorders are summarized. Most of the available drugs interact with the 5-HT_{1A} receptor, the GABA receptor or transporters (SSRI's and SNRI's), while none of the drugs bind to the glucocorticoid receptor or NMDA receptor. These receptors could be interesting targets, since corticosteroids are assumed to be the main neurotransmitters which, after long-term exposure, could lead to psychiatric disorders.

§4.1 The GR as new target

Kamal et al. points out that the hippocampus has a major role in learning and memory, but is also one of the most affected structures in the stress response. The hippocampus shows dense expression of glucocorticoid receptors among others. Elevated levels of corticosterone leads to increased density of GRs. Excessive activation of GRs is associated with changes in hippocampal structure and impairments in functioning of the hippocampus at cellular and behavioral levels.



The article of Kamal et al. showed that during social isolation corticosterone levels significantly increased, leading to depressed induction of long-term potentiation (LTP). The same depressed induction was seen when socially housed mice recieved chronic corticosterone infusion, indicating that corticosterone is responsible for depressed induction of LTP. Infusion of GR antagonist RU38486 (mefistiprone) restored the LTP-impairments in isolated mice. This suggests that increased levels of corticosterone at via the GR and that administration of GR antagonist RU38486 is able to retore the effects of corticosterone (Figure 8) [Kamal et al. 2014].

Figure 8, adapted from Kamal et al., showing that social isolation (SI) leads to LTP impairment compared to socially housed (SH) mice. Treatment of the SI-mice with the GR antagonist mefipristone (RU38486) rescued the LTP impairments after social isolation to levels comparable with SH-mice.

Other studies also confirmed that mifepristone is able to reverse suppresion of neurogenesis caused by corticosterone [Mayer et al. 2006, Oomen et al. 2007, Hu et al. 2012]. If a GR antagonist is able to restore the effects of corticosterone, then this antagonist could possibly be used as a treatment in PTSD patients, who suffer from long-term elevated levels of cortisol.

The GR antagonist mifepristone is already approved by the FDA for Cushing's Syndrome after Castinetti et al. and Fleseriu et al. showed effectiveness in 2009 and 2012 respectively. Recently, the FDA approved mifepristone as a treatment for hyperglycemia in adults with Cushing's Syndrome [FDA website].

The studies of Kamal et al. and others [Mayer et al. 2006; Oomen et al. 2007; Hu et al. 2012] indicate that mifepristone is able to restore the effect of elevated levels of corticosterone, which is also found during chronic stress. Therefore, a GR antagonist as mifepristone could be an innovative therapy for PTSD patients, who suffer from chronic stress and elevated levels of corticosterone. With a GR antagonist, brain damage can be prevented, and possibly even restored.

§4.2: The NMDAR as new target

Stahl describes in *Essential Psychopharmacology* that excessive glutamate release could lead to neural damage in schizophrenic patients. Therefore, the idea has arisen that blocking excessive glutamate neurotransmission with NMDAR antagonists might prevent damage or death to neurons in schizophrenia. Katalinic et al. describes that ketamine, a NMDAR antagonist, showed quick and significant improvement in mood in most of the patients, although these effects have been found for only a short duration. More research is necessary to find the optimal dose and route of administration, and maybe a solution to the short duration of the effect. But, NMDAR antagonists such as PCP or ketamine could also cause or worsen positive or cognitive symptoms [Stahl, 2008, p.440]. Therefore, less robust NMDA antagonists such as memantine might be better a option since these drugs block NMDA neurotransmission only partially.

A study of Paraschakis (2014) showed that memantine improved mood in a schizophrenic patient, and even after remission positive symptoms remained. A study of Koola et al. also indicates that memantine leads to mood improvement in shizophrenic patients, and that a combination of memantine and galantamine is even more effective. Galantamine improves AMPA-mediated signaling, which could lead to more neuroprotection and memory improvement. Grados et al. compared several glutamate-modulating drugs in obsessive-compulsive disorder (OCD) and found mood improvement in 43% to even 89% of the OCD patients after treatment with memantine compared to the control group. These results indicate that memantine is able to improve mood in schizophrenic or OCD patients by partially blocking the NMDA receptor.

For PTSD patients, NMDAR antagonists could protect the hippocampus from neurotoxicity by glutamate, and could therefore be interesting drugs for PTSD patients. More research is necessary to determine whether NMDAR antagonists as ketamine or PCP can be used, or partial antagonists are more optimal as indicated by Paraschakis (2014), Koola et al. and Grados et al.. Koola et al. even proposes a combination therapy of memantine and galantamine to improve memory and neuroprotection.

This chapter described the possibility of using the GR and NMDAR as innovative targets for PTSD treatment. Mifepristone, a GR antagonist, has shown to restore the effects of elevated levels of corticosterone [Kamal et al. 2014] and could therefore be an interesting drug for PTSD treatment. For the NMDA receptor, several antagonists are known that could inhibit the harm causing effects of glutamate. Full antagonists as ketamine and PCP are known and already used in schizophrenia because they prevent damage or death to neurons, but both antagonists could also worsen the symptoms of schizophrenia [Stahl, 2008, p.440]. Therefore, partial NMDAR antagonists such as memantine could be more useful, preventing the neural damage without worsening the schizophrenic symptoms [Grados et al. 2013; Paraschakis 2014]. Koola et al. even proposes a combination therapy of memantine and galantamine. More research is necessary to confirm these results, and to determine the best NMDA antagonist, maybe even in combination with a AMPA-pathway stimulator as galantamine.

Discussion

This review described the stress-responses of the body and the risks of chronic stress. The quick stress response activates the sympathetic nervous system leading to release of adrenaline and noradrenaline [Rang & Dale, 2008, p.168] and the slow stress response activates the HPA axis leading to release of corticosteroids [Gillies et al. 1982]. The amygdala, PFC and hippocampus are the brain regions affected by these stress hormones, especially by corticosteroids, leading to neural growth in the amygdala and neuron atrophy in PFC and hippocampus [McEwen, 2000]. These effects lead to brain damage and eventually to stress-related disorders like anxiety, depression or posttraumatic stress syndrome (PTSD). PTSD was highlighted since less medication is available for patients suffering from this disorder. Studies in PTSD confirmed that longterm exposure of glutamate and corticosteroids caused by chronic stress were responsible for brain damage in PTSD patients, particularly in the hippocampus [Sapolsky et al. 1990; McEwen and Sapolsky 1995]. The GR and NMDAR are highly expressed in the affected brain regions and overactivation of both receptors will result in neural damage, by glutamate via the NMDA receptor or by corticosteroids via the glucocorticoid receptor. Remarkably, none of the available medication for PTSD targets corticosteroids or glutamate. SSRI's and TCA's are able to induce noradrenaline and serotonin and thereby able to reduce anxiety and depression, but these drugs cannot prevent or restore neural damage caused by corticosteroids or glutamate. Thus, the available drugs are able to reduce the symptoms of stress-related disorders, but not the neural damage. Therefore, the glucocorticoid- and NMDA receptors could be innovative targets for PTSD medication, in order to prevent or even restore brain damage, which would otherwise lead to lasting consequences.

Several research groups performed experiments with (partial) antagonists for these receptors in schizophrenic and OCD patients, and showed to be effective. Mifepristone, a GR antagonist, has shown to restore the effects of elevated levels of corticosterone [Kamal et al. 2014] and could therefore be an interesting drug for PTSD treatment. For the NMDA receptor, several antagonists are known that could inhibit the harm causing effects of glutamate. Full antagonists as ketamine and PCP are known and already used in schizophrenia because they prevent damage or death to neurons, but both antagonists could also worsen the symptoms of schizophrenia [Stahl, 2008, p.440]. Therefore, partial NMDAR antagonists such as memantine could be more useful, preventing the neural damage without worsening the schizophrenic symptoms [Grados et al. 2013; Paraxchakis 2014]. Koola et al. even proposes a combination therapy of memantine and galantamine, since galantamine stimulates the AMPA-pathway to improve memory and neuroprotection. More research is necessary to confirm these results, and to determine the best NMDAR antagonist, maybe even in combination with a AMPA-pathway stimulator as galantamine. Therefore, clinical studies need to be performed, showing efficacy of GR antagonist mifepristone in PTSD patients. Next to that, a clinical study concerning the NMDAR should be designed. The study should compare memantine, memantine and galantamine and a control group in PTSD patients, to show efficacy of memantine and a combination of memantine and galantamine. This study will also indicate wether memantine should be administered alone or in combination with galantamine.

These different pathways and combination therapies indicate that mental disorders like schizophrenia or PTSD are more complex than expected and it is possible that in the future, combination therapies are necessary to treat these complex disorders. Nevertheless, antagonists for the GR and NMDAR are crucial, since none of the available drugs for PTSD are able to prevent or maybe even restore neural damage. The fact that neural damage is a longlasting or permanent condition only subscribes the need for GR and/or NMDAR antagonists.

At the same time, the value of psychological treatment should be taken into account. Gillies et al. (2012) examined the effectiveness of psychological treatment in children and adolescents diagnosed with PTSD. Their review described that in several studies significant improvement was found, since the symptoms were significantly lower within a month of psychological therapy compared to a control group. The longer a patient recieves therapy, the more reduction of the symptoms was found. This indicates that patients benefit from psychotherapy to learn to cope with chronic stress (think of emotion regulation and relaxation). According to the FDA [FDA website]and van Loenen [2008, p.60], the main therapy for PTSD patients is psychotherapy, and medication can be prescribed as a support. Nevertheless, psychotherapy treats depression or traumatic symptoms, but doesn't inhibit neurotoxic effects of excessive glutamate or cortisol levels. A combination of psychotherapy and a GR – and/or NMDAR antagonist to prevent or restore brain damage might therefore give best results for PTSD patients.

In conclusion, this review was written in order to point out the huge effects of chronic stress on several brain regions, namely neural death and stress-related disorders. After making an overview of stress-related disorders, it seemed that hardly any medication is available for PTSD patients. Next to that, it was shown that the available medication is able to reduce the depression or anxiety, but not able to prevent or restore the brain damage caused by corticosteroids and glutamate while brain damage could lead to lasting effects. Antagonists for the proposed innovative targets, namely the GR and NMDAR, could prevent or possibly even restore this brain damage and thereby contribute to an improved quality of life of PTSD patients. In schizophrenia, antagonists for these receptors are already used and showed to be effective. Clinical studies are proposed to determine whether mifepristone, memantine, galantamine or even a combination therapy shows efficacy in PTSD patients. At the same time, the value of psycological treatment should not be underestimated. Additional psychotherapy could possibly even lead to recovery of PTSD patients. It may be clear that the GR and NMDAR are important targets in PTSD, and that medication based on antagonizing the actions of these receptors leads to reduction of brain damage in PTSD and possibly even to recovery.

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