Corticosteroid effects on glutamatergic transmission and fear memory
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Chapter 1

Tuning hippocampal synapses by stress-hormones: relevance for emotional memory formation

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Abstract

While stress is often associated with an increased risk to develop (psycho) pathology, the initial response after exposure to stressors is often highly beneficial and allows individuals to optimally cope with challenging situations. Various neurotransmitters and neuromodulators – such as catecholamines and glucocorticoids - are released upon exposure to stressors and regulate behavioural adaptation to stress and enhance the storage of salient information. Studies over the past years have revealed that catecholamines and glucocorticoids regulate synaptic function and synaptic plasticity - which underlie memory formation - in a highly dynamic manner. In this brief review we will summarize how catecholamines and glucocorticoids regulate synaptic function and discuss how these effects may contribute to acquisition and storage of emotional information.
Introduction

Cognitive processes such as attention, perception and storage of information allow individuals to optimally perform in a complex environment such as a society. In any environment however, events or situations can occur which differ in the degree of salience. This requires fine tuning of cognitive processes to adapt to those salient – often important - conditions, by increasing alertness, changing to adequate behavioural strategies and remembering and using information which is relevant for that particular context.

While rapid and persistent alterations in neuronal function, neuronal communication and network function allow behavioural adaptation, the release of hormones and neurotransmitters such as catecholamines (e.g. (nor)adrenaline), corticotropin releasing hormone (CRH) and glucocorticoids during and after stressful and challenging situations are highly capable to facilitate optimal behavioural adaption to salient events (de Kloet et al., 1999; McGaugh, 2004; Joëls et al., 2006; Joëls and Baram, 2009; Roozendaal et al., 2009). The number of neuromodulators that facilitate coping and behavioural adaptation to stressors is large (Joëls and Baram, 2009) and various studies over the past years have provided evidence that several of these modulators steer cellular processes such as synaptic function, synaptic plasticity and activity in networks which are fundamental for attention, perception and learning and memory (Kim and Diamond, 2002; de Kloet et al., 2005; Joëls and Baram, 2009; Hermans et al., 2011). The time frame at which these modulators modify cellular responses, ranging from effects within seconds and minutes to hours, is highly relevant for behavioural adaptation to stressors (Joëls et al., 2011). Although many hormones and neurotransmitters can modify cellular properties and behaviour we will mainly focus in this review on the role of catecholamines (noradrenaline) and glucocorticoid hormones.

Studies in humans and animals show that activation of the autonomic nervous system is one of the earliest responses after exposure to a stressor (Figure 1A). Noradrenaline,
via projections from the Locus Coeruleus, is released in the brain almost immediately after exposure to stressful experiences (de Kloet et al., 2005; Joëls and Baram, 2009). In addition, noradrenaline and adrenaline are released from the adrenal medulla during and after stressful conditions (Figure 1B). Noradrenaline and adrenaline regulate neuronal function via G-protein coupled α and β-adrenergic receptors. Activation of these receptors results in a cascade of cellular responses which involve activation of various kinases such as cyclic AMP (cAMP), Calcium-calmodulin-dependent kinase II (CaMKII) and protein kinase A (PKA) (Hu et al., 2007). Although adrenaline and noradrenaline levels decline within 30-60 minutes after activation of the autonomic nervous system (autonomic nervous system), they can also exert long-lasting genomic actions via activation of for example cAMP response element-binding protein (CREB) (Chai et al., 2014).

Exposure to stressful situations also activates the Hypothalamus-Pituitary-Adrenal (HPA)-axis (de Kloet et al., 2005) (Figure 1A). This involves the release of corticotropin releasing hormone (CRH) from the hypothalamus which stimulates the release of adrenocorticotropin releasing hormone (ACTH) from the anterior pituitary gland and finally the release of glucocorticoids (corticosterone in rodents and cortisol in humans) from the adrenal glands (Figure 1B). Corticosteroid hormones can bind to the high affinity mineralocorticoid receptors (MRs) and lower affinity glucocorticoid receptors (GRs) (de Kloet et al., 2005). These receptors are present in the brain and have been reported to regulate cellular function in the brain within minutes via membrane receptors but they can also have delayed effects - via regulation of gene transcription and protein synthesis – by activating cytosolic receptors (de Kloet et al., 2005; Karst et al., 2005; Tasker et al., 2006; Karst et al., 2010; Pasricha et al., 2011; Liston et al., 2013) (Figure 1C). (Nor)adrenaline and glucocorticoids can therefore regulate cellular function within minutes, but can also exert long-lasting effects which involve protein synthesis (Figure 1B). There is also emerging evidence that (nor)adrenaline and glucocorticoid hormones can interact at the functional level to modify cellular responses (Joëls et al., 2011). We will discuss how (nor)adrenaline and glucocorticoid hormones rapidly but also persistently regulate synaptic function, synaptic plasticity and neuronal activity.
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Figure 1. Stress, synapses and behavioural adaptation

A. Exposure to a stressor activates the Autonomic Nervous system. Noradrenergic projection from the Locus Coeruleus (LC) project to brain areas involved in emotional memory formation. In addition, exposure to a stressor activates the Hypothalamus-Pituitary-Adrenal Axis thereby increasing plasma cortisol (humans) and corticosterone (rodents) levels. These hormones regulate neuronal excitability and behavior via mineralocorticoid receptors (MR) and glucocorticoid receptors (GRs).

B. Stress rapidly increases noradrenaline and glucocorticoid levels.

C. Via their receptors, noradrenaline and glucocorticoid hormones can exert rapid non-genomic as well as genomic actions.

and discuss whether and how these effects may be relevant for memory formation.

Stress-hormones and memory formation

Studies in humans and rodents have revealed that noradrenaline enhances emotional memory formation via activation of β-adrenergic receptors (Cahill et al., 1994; Hu et al.,
In addition, post-training administration of corticosterone – in various emotionally arousing learning tasks (such as Morris Water maze, Fear conditioning, Inhibitory avoidance) and in various species (including chicks, mice and rats) enhances the consolidation of emotionally arousing information (Oitzl and de Kloet, 1992; Sandi and Rose, 1994; Pugh et al., 1997a; b; Oitzl et al., 2001; Zhou et al., 2010). Various lines of evidence suggest that activation of GRs promotes consolidation via genomic actions (Oitzl et al., 2001), although these effects might also be mediated via glucocorticoids acting via membrane GRs (Roozendaal et al., 2010). In addition to the role of GRs, also MRs have been implicated in memory formation. Human and rodent studies show that stress causes a transition from using hippocampus-dependent spatial strategies to striatum-dependent habitual learning (Schwabe et al., 2010; 2012). These studies suggest that stress hampers (more flexible) spatial learning and enhances stimulus-response learning, which might promote adaptation and survival by relying on learned automated behaviour when exposed to acute stressors. This switch in behavioral strategies is mediated by MRs (Schwabe et al., 2010). Finally, catecholamines and glucocorticoids (via activation of GRs) also interact to optimally promote memory consolidation (Roozendaal et al., 2006; 2009).

Synapses and memory formation

An important question that needs to be addressed is how catecholamines and glucocorticoid hormones (alone and together) regulate learning and memory. Synaptic plasticity - the ability of synapses to change their strength in response to altered activity in synaptic pathways - is a major cellular substrate for learning and memory and behavioural adaptation (Malinow and Malenka, 2002). Long-term potentiation (LTP) and long-term depression (LTD) are two major forms of synaptic plasticity and reflect lasting increased and decreased synaptic transmission respectively (Abraham and Williams, 2008). Both LTP and LTD have been implicated in learning and memory (Neves et al., 2008). This evidence is based on studies demonstrating the targeting molecular mechanisms that underlie synaptic plasticity (often) also affect learning and memory (Rumpel et al., 2005; Neves et al., 2008; Kessels and Malinow, 2009;
Mitsushima et al., 2011); that changes in synaptic plasticity during the learning process e.g. (Rogan et al., 1997; Whitlock et al., 2006) and the notion that occlusion of synapses hampers memory processing (Moser et al., 1998; Whitlock et al., 2006). A recent study further demonstrated the link between LTP, LTD and memory from (Nabavi et al., 2014). By using fear conditioning paradigm and optogenetic tools, they showed that fear conditioning, a type of associative memory, can be inactivated and reactivated by LTD and LTP respectively, which is direct evidence of the link between synaptic processes and memory.

Plasticity at synapses can be regulated in two ways: (1) at the presynaptic site by changing the release of neurotransmitter molecules; (2) at the postsynaptic site by changing the number, types, or properties of neurotransmitter receptors (Kessels and Malinow, 2009; Huganir and Nicoll, 2013). In particular AMPA receptors and NMDA receptors have been implicated in synaptic plasticity. During LTP induction, activation of NMDARs by glutamate, in concurrence with depolarization of the postsynaptic membrane relieves the magnesium channel block which allows the entry of calcium through the NMDARs and results in increased intracellular calcium levels (Nicoll and Malenka, 1998). Calcium activates various kinases that in turn regulate the number and properties of synaptic AMPA receptors. AMPA receptors mediate basal synaptic transmission and consist of four major core subunits (GluA1-4) that form heteromeric tetrameric complexes (Traynelis et al., 2010), although also homomers have been reported in the brain (Plant et al., 2006). The major AMPA receptor isoforms are GluA1/2 and GluA2/3 AMPARs (Lu et al., 2009). Studies from the past years have shown that these subunits (GluA1-4) are phosphorylated at serine, threonine, and tyrosine residues by several protein kinases including CaMKIIα, Protein Kinase A, Protein Kinase C, Protein Kinase G, tyrosine kinase FYN, and Jun amino-terminal kinase (JNK) (Shepherd and Huganir, 2007; Lu and Roche, 2012), which highly is important for synaptic transmission and plasticity (Huganir and Nicoll, 2013).

In recent years, substantial evidence has been gathered that AMPA receptor trafficking to and from synapses is involved in LTP and LTD (but see also (Granger et al., 2013)). This
was directly visualized in 1999 using GFP-tagged receptors expressed in organotypic hippocampal slices by using Sindbis virus (Shi et al., 1999). This study showed that GFP-GluA1 was recruited to synapses after LTP induction together with synaptic transmission enhancement. The current view is that AMPA receptors exocytose to endocytic zones at the membrane and traffic to synapses via lateral diffusion (Makino and Malinow, 2009; Petrini et al., 2009; Kennedy et al., 2010), which is stimulated under LTP-like conditions (Makino and Malinow, 2009).

Several lines of evidence indicate that the dynamic regulation of AMPAR is highly relevant for learning and memory. First, learning increases the expression of synaptic AMPARs and results in LTP-like changes (Whitlock et al., 2006). Second, synaptic insertion of AMPARs in amygdala and hippocampal synapses underlies cue and context conditioning respectively (Rumpel et al., 2005; Mitsushima et al., 2011). Third, studies in transgenic mice demonstrate that GluA1 mutant mice are impaired in short-term working memory (Sanderson et al., 2011a; b).

**Stress, synapses and plasticity**

Stress has a major impact on synaptic plasticity and synaptic function. These effects range from enhancing synaptic plasticity to reducing synaptic plasticity. The direction of the effects on synaptic plasticity depend a.o. on timing (i.e. when does stress occur with respect to synaptic stimulation); history of the animal and the nature stress-exposure (brief versus chronic exposure to stress) (Joëls and Krugers, 2007). We will discuss how catecholamines and glucocorticoid hormones regulate synaptic function and synaptic plasticity with a focus on the hippocampal formation, unless stated otherwise.

In vitro and ex vivo studies show that noradrenaline - within minutes after activation of β-adrenergic receptors - activates CaMKII and PKA and increases the phosphorylation of AMPA receptors (Hu et al., 2007). Importantly, this reduces the threshold to evoke synaptic potentiation and facilitates the ability to elicit long-term potentiation (Thomas et al., 1996; Winder et al., 1999; Hu et al., 2007; Tully et al., 2007; Gelinase et al., 2008;
In vitro studies in the hippocampus show that increased corticosterone levels, within minutes, enhances the frequency of mEPSCs and the release of glutamate from presynaptic terminals (Karst et al., 2005; Olijslagers et al., 2008; Pasricha et al., 2011). In the same time domain, corticosterone increases AMPA receptor lateral diffusion in hippocampal primary neurons (Groc et al., 2008). These effects require activation of MRs and may increase within minutes the ability to enhance synaptic plasticity (Wiegert et al., 2006) (Figure 2). At least one hour after brief application, corticosterone enhances AMPA receptor lateral diffusion, AMPA receptor exocytosis and synaptic retention of AMPA receptors. Consequently, AMPA receptor mediated synaptic transmission is enhanced (Karst and Joëls, 2005; Martin et al., 2009). Stress and corticosterone also enhance excitatory synaptic transmission in the prefrontal cortex via activation of and mechanisms which require activation of serum- and glucocorticoid-inducible kinase (SGK) regulation and Rab GTP-ases GRs (Yuen et al., 2009; Liu et al., 2010; Yuen et al., 2011). At this time, approximately one hour after activation of GRs, the activity-dependent synaptic insertion and AMPA receptor mediated synaptic function is occluded ((Groc et al., 2008); Xiong unpublished observations). This supports earlier studies which have demonstrated that brief stress exposure reduces the ability to elicit hippocampal LTP - both when measured in vivo as well as in ex vivo slice preparations (Foy et al., 1987; Shors et al., 1989; Kim et al., 1996; Pavlides et al., 1996) (Figure 2). In the same time domain, glucocorticoid hormones facilitate the ability to induce long-term depression (Coussens et al., 1997; Xu et al., 1997) indicating that corticosteroid hormones can weaken synapses when they receive low frequency input. These studies reveal that glucocorticoid hormones can rapidly facilitate synaptic plasticity, but also – via a slower mode of action – can reduce the ability to elicit LTP.

Importantly, corticosterone and noradrenaline act in synergy not only to enhance memory formation (Quirarte et al., 1997; Roozendaal et al., 2006; 2009). Also at the synaptic level, noradrenaline and corticosterone interact; briefly after co-application, synaptic plasticity (Pu et al., 2007); AMPA receptor mediated synaptic transmission,
AMP A receptor surface expression and phosphorylation of AMPA receptors are enhanced (Zhou et al., 2011; Krugers et al., 2012).

**Stress, synapses and memory**

In the previous paragraphs we have discussed that catecholamines and glucocorticoid hormones rapidly increase the ability to elicit long-term potentiation, which reflects an increased ability to acquire information. Approximately one hour later, the ability to evoke LTP is occluded which might reflect a process to prevent overwriting of already stored information, thereby enabling memory consolidation (Figure 2). An important question is whether the effects of stress and stress-hormones on synapses are relevant for memory formation. Recent studies suggest that the effects of catecholamines and glucocorticoid hormones on synaptic function are causally related. First, the memory enhancing effects of noradrenaline on emotional learning as assessed in a fear conditioning task is critically dependent on phosphorylation of GluA1 containing AMPARs (Hu et al., 2007). Moreover, several behavioural studies support the hypothesis that corticosteroid hormones regulate memory via mechanisms that underlie synaptic plasticity such as the MAPK pathway, synapsin-la/1b and CaMKII (Revest et al., 2005; 2010; Chen et al., 2012; Revest et al., 2014) and enhance memory formation via regulation of AMPA receptors at excitatory synapses (Conboy and Sandi, 2010). In the Morris water maze synaptic insertion of AMPARs is required for memory enhancing effects of learning under stress (Conboy and Sandi, 2010). Finally, there is substantial evidence that corticosteroid hormones regulate memory formation that requires prefrontal cortex function via AMPA receptors (Yuen et al., 2009; 2011).

**Early life experience and sensitivity of synapses**

Early life adversity has profound effects on cognitive function such as learning and memory. In general, early life adversity hampers spatial learning but enhances emotional memory formation (Champagne et al., 2008; Oomen et al., 2010). Early life adversity has also substantial and long lasting effects on synaptic function and
plasticity. Low levels of maternal care and chronic early life stress reduce synaptic potentiation in the hippocampus (Brunson et al., 2005; Champagne et al., 2008; Bagot et al., 2009; 2012) while increasing NMDA receptor mediated synaptic transmission (Bagot et al., 2012; Rodenas-Ruano et al., 2012). Interestingly, early life adversity alters the sensitivity of synapses for stress and stress-hormones. While corticosterone - hours after administration (or release) usually hampers the ability to elicit synaptic plasticity, several studies indicate corticosterone (and activation of beta-adrenergic receptors) enhances synaptic plasticity in animals with low levels of maternal care (Champagne et al., 2008; Bagot et al., 2009) or in animals which have been exposure to maternal deprivation (Oomen et al., 2010).

**Summary and perspective**

In this review, we summarized recent evidence that stress – via activation of catecholamines and glucocorticoid hormones regulate synaptic plasticity and regulate...
learning and memory. These studies suggest that noradrenaline and corticosterone (in interaction) affect emotional memory formation via dynamically regulating AMPARs. A number of critical questions are important to address in the future.

1) Activity-dependent regulation of glutamatergic receptors
While studies showing that corticosterone and noradrenaline dynamically regulate AMPARs, it remains to be determined how corticosterone and noradrenaline regulate activity-dependent changes in AMPA receptor and NMDA receptor function. Moreover, although many proteins are involved in careful regulation of AMPA and NMDA receptors at the membrane and synapse (Anggono and Huganir, 2012; Huganir and Nicoll, 2013) detailed knowledge on how stress and stress-hormones regulate AMPA and NMDA receptor function is lacking.

2) Region specific effects of stress and stress-hormones
Many studies on stress, stress-hormones and synaptic plasticity have focused on the hippocampus. It is important to note that stress hormones have different effects on synaptic plasticity along the rostro-caudal axis (Maggio and Segal, 2007; 2009). It will therefore be important to examine how stress and stress-hormones regulate synaptic function and plasticity in various brain regions which are involved in memory formation (Karst et al., 2010).

3) Behavioural relevance
Ultimately, it will be essential to understand how regulation of excitatory synapses underlie the effects of stress and stress-hormones on (the different phases of) memory formation (such as acquisition and consolidation) as well as on processes such as attention, perception, habit learning, behavioural flexibility and decision making.

4) Early life experience and synapses
Early life experiences lastingly program behavioural programs, synaptic plasticity and the sensitivity of synapses for stress/hormones. Understanding how early life adversity determines the sensitivity of synapses for stress-hormones will contribute to our
fundamental understanding of individual variation in behavioral adaptation to stressful events (Champagne et al., 2008) and is crucial for a better insight in the development of stress-related psychopathology.
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