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Review

Learning under stress: A role for the neural cell adhesion molecule NCAM

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ABSTRACT

Stress is known to be a potent modulator of brain function and cognition. While prolonged and/or excessive stress generally exerts negative effects on learning and memory processes, acute stress can have differential effects on memory function depending on a number of factors (such as stress duration, stress intensity, timing and the source of the stress, as well as the learning type under study). Here, we have focused on the effects of 'acute' stress, and examined the literature attending to whether the "source of stress" is 'intrinsic' (i.e., when stress is originated by the cognitive task) or 'extrinsic' (i.e., when stress is induced by elements not related to the cognitive task). We have questioned here whether the neural cell adhesion molecule of the immunoglobulin superfamily (NCAM) contributes to the neurobiological mechanisms that translate the effects of these two different stress sources into the different behavioral and cognitive outcomes. NCAM is a cell adhesion macromolecule known to play a critical role in development and plasticity of the nervous system. NCAM and its post-translational modified form PSA-NCAM are critically involved in mechanisms of learning and memory and their expression levels are known to be highly susceptible to modulation by stress. Whereas available data are insufficient to conclude as to whether NCAM mediates extrinsic stress effects on learning and memory processes, we present systematic evidence supporting a key mediating role for both NCAM and PSA-NCAM in the facilitation of memory consolidation induced by intrinsic stress. Furthermore, NCAM is suggested to participate in some of the bidirectional effects of stress on memory processes, with its enhanced synaptic expression involved in facilitating stress actions while its reduced expression being related to impairing effects of stress on memory function.

1. Introduction

Stress can be regarded as an adaptive reaction which helps an organism to cope and respond to changes and to challenging situations. Such stressful situations, in which homeostasis is challenged physically and psychologically, initiate an activation of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, the latter resulting in increased glucocorticoid blood levels (Kim & Diamond, 2002).

Whereas brief activation of stress responses can have beneficial consequences for the organism, such as mobilization of energy resources and suppression of immune responses, prolonged or extensive stress have a negative influence on most physiological systems (McEwen, 2002). Increasing evidence also points out that inappropriate stress responses and/or control might be associated with the development of physiological alterations and neuropsychiatric disorders (de Kloet, Joels, & Holsboer, 2005; Heim & Nemeroff, 1999; Mazure, Kincare, & Schaffer, 1995; McEwen, 2005; Sandi & Bisaz, 2007; Wiedenmayer, 2004).

Extensive research carried out during the last decades has shown that stress is a potent modulator of brain function and cognition (de Kloet, Oitzl, & Joels, 1999; Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Kim & Diamond, 2002; Kim & Haller, 2007; McEwen, 1999; Sandi, 2004; Sandi & Pinelo-Nava, 2007). In particular, learning and memory processes have been shown to be highly susceptible to modulation by stress. Although the common message derived form this field of stress research is that stress is detrimental for an organism, a substantial number of studies have illustrated that stress can also have a facilitating effect on learning and memory formation. In fact, a myriad of actions have been reported for stress – including impairing and facilitating effects, as well as no effects – on memory function that have prompted the need to categorize factors around both stress and memory and to dissect the nature of their interactions to specific conditions (for reviews, see de Kloet et al., 1999; Diamond, Campbell, Park,

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Halonen, & Zoladz, 2007; Kim, Song, & Kosten, 2006; Roozendaal, 2002, 2003; Roozendaal, Barsegyan, & Lee, 2008; Sandi, 1998).

In a recent review (Sandi & Pinelo-Nava, 2007), we have emphasized the importance of taking into account a number of key factors in order to progress our understanding of the impact of stress on memory function. One of those critical factors is "stress duration" and our review of the literature (Sandi & Pinelo-Nava, 2007) showed the need to distinguish between 'acute' and 'chronic' stress situations, particularly for their demonstrated differential impact on the acquisition of information. Here, we will focus this review to the effects of 'acute' stress, since the generally deleterious effects of 'chronic' stress on learning and memory have been reviewed to a great extent in the literature (Joels et al., 2004; McEwen, 1999, 2005; Sandi, 2004).

When focusing on *acute* stress, one of the factors that appears to be critical is the "source of stress", which makes reference to the origin of stress with regard to the cognitive task or, in other words, to stress (or stress hormone activation) contingency to the particular information processing under study (de Kloet et al., 1999; Joels et al., 2006; Sandi, 1998). To dissect this factor into elements, we (Sandi & Pinelo-Nava, 2007) have introduced the terminology of 'intrinsic stress', referring to the situations in which stress is originated by elements related to the cognitive task, and 'extrinsic stress', referring to those situations in which stress is originated by conditions completely unrelated to the cognitive task (i.e., the outside world) and thus generally occurring temporally dissociated from such task (i.e., either before or afterwards). Generally, *intrinsic* stress seems to facilitate memory consolidation processes (Joels et al., 2006; Sandi, 1998; Sandi & Pinelo-Nava, 2007) with stress hormones (glucocorticoids, noradrenaline) reported to play a key role by exerting their actions within the same neuronal circuits that are activated by the learning experience where they can help to modulate and stabilize such neuronal circuits (Joels et al., 2006; Sandi, 1998). From an evolutionary point of view, the role of *intrinsic* stress would be to help the individual to recognize and remember a potentially threatening situation, allowing a faster and appropriate reaction in future encounters with a similar threat. However, when the source of stress is *extrinsic*, the effects seem to be quite heterogeneous, depending very much on the learning type [note that the "learning type" has also been highlighted as one of the critical factors to take into account for the understanding of the nature of stress and memory interactions (Sandi & Pinelo-Nava, 2007)] under study (Kim & Diamond, 2002; Roozendaal, 2002; Sandi & Pinelo-Nava, 2007) and on the timing of the stress experience in regard to the information processing (Sandi & Pinelo-Nava, 2007).

In addition to understanding the modulatory effects of stress on memory function, one of the challenges of the field is to decipher the neurobiological mechanisms that translate the effects of stress into the different behavioral and cognitive outcomes. Memory function is nowadays believed to involve the remodeling of neural circuits (Martin, Grimwood, & Morris, 2000; Martin & Morris, 2002; Morris, 2006; Morris et al., 2003) which places an important role on processes linked to synaptic mechanisms. In this context, the neural cell adhesion molecules (NCAM), a member of the immunoglobulin superfamily, that shape the formation of neuronal networks during development and is critically involved in adult synaptic plasticity, has been shown to play a critical role in memory formation (Conboy, Bisaz, Markram, & Sandi, in press).

In this review, we will revise the related literature to question whether NCAM and its polysialylated form (PSA-NCAM) are involved in the modulatory effects that acute stress exerts in memory function. We will address this issue by separately considering situations related to intrinsic and to extrinsic stress. But before addressing these questions, we will start by giving a brief introduction about the role of NCAM and PSA-NCAM in neural and synaptic plasticity.

2. The role of NCAM on synaptic plasticity

Neuronal CAMs of the immunoglobulin (Ig) superfamily are multidomain proteins with a key role in neural development, including axonal extension and guidance, cell migration, differentiation, survival, synaptogenesis and synaptic stabilization (Kiss & Muller, 2001; Maness & Schachner, 2007; Muller et al., in press; Rougon & Hobert, 2003). Among the variety of family members, we focus here on NCAM, as in addition to its involvement in neurodevelopment, has also been largely implicated in synaptic plasticity and cognitive processes in adulthood. NCAM seems to participate in the modulation of both short-lasting plasticity at pre-existing synapses and long-lasting plasticity linked to synaptic formation and/or elimination (Fields & Itoh, 1996; Kiss & Muller, 2001; Schachner, 1997). Moreover, genetic epidemiological studies in humans and cumulative evidence in rodents have pointed out a critical role for this molecule in learning and emotion (for a review, see Conboy et al., in press).

2.1. NCAM

NCAM is expressed in the vertebrate nervous system as three main isoforms generated by alternative splicing from a single gene: NCAM-120, NCAM-140, and NCAM-180 (their names standing for their relative molecular weights) (Cunningham et al., 1987; Walmod, Kolkova, Berezin, & Bock, 2004). Extracellularly, all isoforms bear five Ig-like modules and two fibronectin type III modules. Current knowledge about the functional roles of NCAM supports the view that interfering (i.e, blocking or impairing) with NCAM function can lead to cognitive impairments and emotional alterations (Conboy et al., in press).

Pioneer work showed that induction of long-term potentiation (LTP, regarded as an electrophysiological model of learning and memory formation) is inhibited by administration of antibodies against NCAM or of synthetic peptides able to interrupt NCAM adhesion (Lüthi, Laurent, Figurov, Muller, & Schachner, 1994; Ronn, Bock, Linnemann, & Jahnsen, 1995). Conversely, administration of another synthetic peptide, the NCAM-derived mimetic peptide, FG loop (FGL), which mimics NCAM activation of the fibroblast growth factor receptor 1 (FGFR1), was recently shown to effectively attenuate age-related impairment in LTP by its anti-inflammatory effect on activated microglial cells (Downer et al., in press). Deletion of the NCAM gene in NCAM knock-out (NCAM KO) mice leads to impaired LTP at CA1 and at mossy fiber synapses in CA3 hippocampal areas (Cremer et al., 1998; Muller et al., 2000). In addition, NCAM KO mice have been reported to show severe cognitive impairments and emotional alterations, including: (i) impaired spatial learning and memory (Cremer et al., 1994; Stork et al., 2000), (ii) impaired auditory and contextual fear conditioning (Senkov et al., 2006; Stork et al., 2000), (iii) impaired odor discrimination (Gheusi et al., 2000), (iv) enhanced anxiety (Cremer et al., 1994; Stork, Welzl, Cremer, and Schachner, 1997; Stork et al., 1999), (v) reduced footshock sensitization in the startle response (Plappert, Schachner, & Pilz, 2006), (vi) enhanced exploratory behavior (Stork, Welzl, Cremer, & Schachner, 1997; Stork et al., 1999), (vii) enhanced inter-male aggression towards an intruder (Stork et al., 1997, 2000) and (viii) increased corticosterone levels following social intruder stress (Stork et al., 1997). Moreover, these NCAM KO mice show also mild morphological alterations in the CNS, including a reduction in brain weight and size of the olfactory bulb (Cremer et al., 1994) and an altered cytoarchitecture of

the hippocampus (Cremer, Chazal, Goridis, & Represa, 1997; Tomasiewicz et al., 1993).

2.2. NCAM polysialylation (PSA-NCAM)

One important post-translational modification of NCAM is its glycosylation consisting of the addition of extended chains of the carbohydrate α2,8-linked polysialic acid (PSA). PSA modulates cell–cell interactions through its attachment to NCAM by reducing homo- and heterophilic NCAM adhesive activities (Cunningham, Hoffman, Rutishauser, Hemperly, & Edelman, 1983; Johnson, Fujimoto, Rutishauser, & Leckband, 2005; Rutishauser, 1998; Sadoul, Hirn, Deagostini-Bazin, Rougon, & Goridis, 1983). PSA-NCAM is highly expressed during brain development and its levels gradually decrease during the early post-natal period (Angata & Fukuda, 2003; Rutishauser, 2008). In the adult brain, high levels of PSA-NCAM remain restricted to specific regions that either retain neurogenic capacity, such as the subventricular zone and the granular cell layer of the hippocampus, or that exhibit physiological plasticity, such as regions of the hypothalamus, the entorhinal–hippocampal complex and the thalamus (Bonfanti, 2006; Gascon, Vutskits, & Kiss, 2007; Rutishauser, 2008). PSA is synthesized by two polysialyltransferases ST8SiaII/STX (Kojima et al., 1996; Scheidegger, Sternberg, Roth, & Lowe, 1995) and ST8SiaIV/PST (Eckhardt et al., 1995; Nakayama, Fukuda, Fredette, Ranscht, & Fukuda, 1995). Both polysialyltransferase mRNAs are coexpressed, but they differ markedly with respect to their spatial and temporal expression patterns. While ST8SiaII/STX is predominantly expressed in the embryo and the early post-natal brain, ST8SiaIV/PST is the form mainly expressed in the adult brain (Hildebrandt, Becker, Murau, Gerardy-Schahn, & Rahmann, 1998).

PSA-NCAM has been implicated in cell migration, axonal regeneration, neuronal survival and synaptic plasticity (Cremer et al., 2000; Dityatev et al., 2004; Kiss, Troncoso, Djebbara, Vutskits, & Muller, 2001). Changes in PSA expression associated with learning and memory consolidation have been observed in the dentate gyrus of the hippocampus (Doyle, Nolan, Bell, & Regan, 1992a; Merino, Cordero, & Sandi, 2000; Murphy, O'Connell, & Regan, 1996; Murphy & Regan, 1998; Sandi et al., 2003), in subregions of the amygdala complex (Markram, Lopez Fernandez, Abrous, & Sandi, 2007b), and the entrohinal/perihinal cortices (Fox et al., 2000; O'Connell et al., 1997). Enzymatic removal of PSA, by PSA-specific endoneuraminidase (endo-N), results in complete loss of LTP and LTD induction *in vitro* (Muller et al., 1996), and in vivo to impaired learning and memory formation (Becker et al., 1996; Lopez-Fernandez et al., 2007; Venero et al., 2006).

Mice with a deletion of the ST8SiaIV/PST gene (ST8SiaIV/PST KO) exhibit normal development and morphological features but show a specific loss of PSA in the dentate gyrus and hilus regions as well as in the entire CA1 and CA3 subfield. This loss is accompanied by impairments of synaptic plasticity (LTP and LTD) at the Schaffer collateral CA1-synapses in the adult, but not in young animals. Interestingly synaptic plasticity in CA3 region remains unaltered in ST8SiaIV/PST knock-out mice (Eckhardt et al., 2000). This age dependent differences in synaptic plasticity is due to the fact that young ST8SiaIV/PST KO mice still express some PSA-NCAM through the second polysialyltransferase ST8SiaII/STX, which is almost not expressed in the adulthood (Hildebrandt et al., 1998). Adult ST8SiaIV/PST KO mice show also some behavioral alterations like a mild impairment in contextual fear conditioning, while auditory fear conditioning remains normal (Markram, Gerardy-Schahn, & Sandi, 2007a; Senkov et al., 2006), and impaired spatial learning (Markram et al., 2007a). Mice with a knock-out of the other ST8SiaII/STX gene display normal synaptic plasticity (LTP) in CA1 and CA3 of the hippocampus, but have an alteration of axonal targeting in the infrapyramidal mossy fibers of the hippocampus. These morphological changes could be in part responsible for the altered behavior of these mice, such as the impaired passive avoidance learning, the hyperactivity in an open field test and reduced fear conditioning to auditory and contextual stimuli (Angata et al., 2004).

3. Stressful learning, as a model of intrinsic stress, and NCAM

Most of the tasks currently used to investigate learning and memory in laboratory rodents can be considered as being stressful for the animals: they are based on the application of stressful manipulations and/or stimuli to motivate animals to learn. As a consequence of their aversive nature, these stimuli elicit the activation of stress systems during training and testing (Aguilar-Valles et al., 2005; Akirav et al., 2004; Cordero, Merino, & Sandi, 1998; Oitzl & de Kloet, 1992). These tasks, in which learning occurs under stressful conditions, include – among others – procedures in which learning is induced by means of applying footshocks, such as in classical (fear) conditioning to a cue and/or a context, passive and active avoidance. In the water maze task, spatial learning and memory is motivated by exposing animals to a tank filled with water from which the only possible escape would be to find a hidden platform.

As indicated above, physiological stress responses elicited by learning situations can contribute to the learning-triggered processes of memory formation (de Kloet et al., 1999; Joels et al., 2006; Sandi, 1998; Sandi & Pinelo-Nava, 2007; Wiegert, Joels, & Krugers, 2008). The clearest and by far best illustrated example for the contribution of intrinsic stress on memory function is on the consolidation mechanisms, while its effect on acquisition and retrieval processes are still not well understood. In this subsection, we will question whether NCAM plays a role in the modulation of memory consolidation mechanisms exerted by stress. But before tackling that question, we will firstly give a brief account of the lines of evidence that have established a role for stress on memory consolidation.

First, modulating the intensity of stress experienced during the learning task (training) can have a strong impact on the strength with which the memory for the acquired information is established. For example, with regards to fear conditioning, a linear relationship between stress intensity at training (by modulating the shock intensities) and the consolidation of fear conditioning has been proposed, with higher stress intensities corresponding to stronger memories (though an asymptotic wave form would account for high-to-very-high stress intensities) (Cordero & Sandi, 1998; Laxmi, Stork, & Pape, 2003; Merino et al., 2000; Revest et al., 2005; Sandi & Pinelo-Nava, 2007; Sandi et al., 2003). A similar linear relationship between stress intensities during training (by varying the water temperature) and the strength of memory formation has also been proposed for spatial learning experiences (Akirav, Sandi, & Richter-Levin, 2001; Sandi, Loscertales, & Guaza, 1997), while the impact of very high stressors is still uncertain since not a single study has included a wide range of stressors intensities in this sort of tasks. In any case, since high stressors during the learning task lead to stronger spatial memories than low stressors, a facilitating effect of stress can be hypothesized.

Further evidence for a role of stress on memory consolidation has been provided by numerous studies that have shown correlational and causal relationships between training-related glucocorticoid levels and the strength of the memory formed. Again a linear relationship has been reported for post-training corticosterone levels as a function of the stress intensity applied at training (and remember that, as just noted in the previous paragraph, stress

intensity is similarly related to the strength of memory formed) (Akirav et al., 2001, 2004; Cordero et al., 1998; Merino et al., 2000; Sandi et al., 1997, 2003). Further, inhibition of either training-induced glucocorticoid secretion (through adrenalectomy or by administration of inhibitors of glucocorticoid synthesis) or of its action through central glucocorticoid receptors (via administration of specific receptor antagonists) has proved to impair memory formation for a number of tasks, including passive avoidance (Roozendaal, Williams, & McGaugh, 1999), contextual fear conditioning (Cordero, Kruyt, Merino, & Sandi, 2002; Cordero & Sandi, 1998), and spatial learning in the water maze (Akirav et al., 2004; Oitzl & de Kloet, 1992; Roozendaal, Bohus, & McGaugh, 1996; Roozendaal & McGaugh, 1997). Conversely, administration (systemic or central) of glucocorticoids or synthetic glucocorticoid receptor agonists either before or shortly after a particular learning task was repeatedly shown to facilitate subsequent retention for a variety of tasks, including passive avoidance (Cabib et al., 1996; Roozendaal & McGaugh, 1996; Sandi, Rose, Mileusnic, & Lancashire, 1995), brightness discrimination (Micheau, Destrade, & Soumireu-Mourat, 1984), contextual fear conditioning (Cordero & Sandi, 1998; Revest et al., 2005), eye-blink conditioning (Beylin & Shors, 2003) and water maze learning (Akirav et al., 2004; Sandi et al., 1997).

We will question now whether NCAM is involved in these stressful learning tasks. The first experimental evidence showing a modulation of NCAM following stressful learning comes from studies on PSA-NCAM expression in rats. A transient, time-dependent increase in hippocampal NCAM polysialylation was repeatedly reported to occur around 10–12 h following training in passive avoidance (Doyle et al., 1992a; Fox, O'Connell, Murphy, & Regan, 1995), water maze (Murphy, O'Connell, & Regan, 1996; Sandi et al., 2003, 2004) and contextual fear conditioning (Sandi et al., 2003) tasks. In several studies, this was localized to a defined population of granule-like cells at the border of the granule cell layer and hilus of the rat dentate gyrus. Although a significant proportion of the polysialylated dentate neurons have been suggested to be *de novo* granule cell precursors (Seki & Arai, 1993), training-induced modulations of PSA-NCAM cannot only be ascribed to neurogenesis (Foley et al., 2008; Fox, O'Connell, Murphy, & Regan, 1995). Hippocampal upregulation of PSA-NCAM has been related to the formation of new, and the remodeling of existing, synapses between certain types of mossy fiber buttons and CA3 pyramidal cells (Seki & Arai, 1999). Interestingly, the highest elevation of PSA-NCAM positive cells in the dentate gyrus of rats trained in water maze was found in animals showing a slower acquisition rate (Sandi et al., 2004), which also display increased anxiety and stress reactivity when confronted with learning the task (Sandi et al., 2004; Venero et al., 2004).

When NCAM polysialylation was evaluated in the dentate gyrus 12 h after training rats at different stressor intensities [high- (1 mA), moderate- (0.4 mA), or low- (0.2 mA) shock intensities] in a contextual fear conditioning task, a differential regulation of PSA-NCAM was observed (Sandi et al., 2003). Whereas rats trained at 0.4 mA had increased numbers of PSA-immunopositive cells and showed also intermediate fear conditioning levels (around 50–70% freezing) in the 12 h retention test, no changes in polysialylated cell frequency were observed in rats trained at a low-shock intensity (0.2 mA). Training at such low-shock intensity does also not induce significant fear conditioning (Sandi et al., 2003). Such findings support the view that training-induced PSA modulation participates in learning-associated synaptic remodeling (Doyle et al., 1992a; Murphy & Regan, 1998). However, evaluation of PSA-NCAM 12 h after training rats at high, 1 mA shock intensity – a condition leading to a more robust and longer-lasting freezing response than lower shock intensities – revealed the opposite pattern; i.e., a decrease in the frequency of polysialylated neurons in the dentate gyrus (Merino et al., 2000; Sandi et al., 2003). Nevertheless, a more complete picture for the 1 mA high stress condition was obtained with a more detailed analysis of hippocampal PSA-NCAM expression levels analyzing separately the dorsal and ventral dentate gyrus 24 h after fear conditioning rats to either the context or a tone. An upregulation of PSA-NCAM expression was found in the dorsal (but not ventral) dentate gyrus after contextual (but not tone) fear conditioning. The causal implication of such upregulation in the memory formed was further confirmed by specific removal of PSA through microinfusion of endo-N that in the dorsal (but not in the ventral) hippocampus reduced freezing responses to the conditioned context (Lopez-Fernandez et al., 2007).

As for PSA-NCAM, the expression pattern of NCAM has also been shown to be influenced after training animals in stressful learning paradigms. For example, when the expression of specific NCAM isoforms was monitored in the dentate gyrus following passive avoidance training, a significant reduction of NCAM-180 was observed 3–6 h post-training, a time-point corresponding to the consolidation phase (Foley et al., 2000). This reduction in NCAM-180 correlated with increased expression of ubiquitin C-terminal hydrolase during the same time period, suggesting that during memory consolidation NCAM undergoes regulated proteolysis by the ubiquitin dependent pathway. A reduction of total NCAM expression was also found 12 h after contextual fear conditioning in the hippocampus of rats that were trained at either low (0.2 mA), moderate (0.4 mA) or high (1 mA) shock intensities (Merino et al., 2000). In contrast, 24 h after training in the contextual fear conditioning paradigm, enhanced NCAM expression was only observed in rats that were trained at 1 mA, but not at 0.2 or 0.4 mA (Merino et al., 2000). The same rats displayed the most pronounced freezing rate in a 24 h memory retention test. Thus, increased NCAM levels 24 h post-training in the hippocampus correlated with the enhanced memory retention observed in animals trained under the highest stress conditions.

The causal implication of such an upregulation of NCAM on the strength of the memory formed was further supported by pharmacological studies in which intracerebroventricularly administered NCAM antibodies were shown to impair spatial learning (Arami, Jucker, Schachner, & Welzl, 1996) and passive avoidance learning (Doyle, Nolan, Bell, & Regan, 1992b; Scholey, Rose, Zamani, Bock, & Schachner, 1993). A direct blockade of glucocorticoid induced memory enhancement was also provoked by administration of NCAM antibodies (Sandi et al., 1995). Similarly, intracerebroventricular injections of a synthetic peptide, C3d, that interferes with NCAM homophilic binding (Cambon, Venero, Berezin, Bock, & Sandi, 2003), either before learning or during the consolidation phase (5–8 h post-training) was shown to impair memory formation in various learning tasks (Cambon et al., 2003; Foley et al., 2000; Hartz, Sohoel, Berezin, Bock, & Scheel-Kruger, 2003; Venero et al., 2006). Conversely, facilitating NCAM function, by administering the peptide FGL [which mimics the activation of the fibroblast growth factor receptor 1 (FGFR1) by NCAM] immediately after fear conditioning or water maze learning, potentiated spatial memory formation (Cambon et al., 2004). Deletion of the NCAM gene was also shown to interfere with spatial learning and memory (Bukalo et al., 2004; Cremer et al., 1994; Stork et al., 2000) and fear conditioning (Senkov et al., 2006; Stork et al., 2000).

Collectively, these findings suggest that the stress component elicited by training leads to the eventual upregulation of NCAM and PSA-NCAM which participate in the neural mechanisms involved in long-term memory storage (for a summary, see Table 1 and Fig. 1). This would fit with previous proposals in the literature of a role for NCAM in the late stages of memory consolidation, in a process that was theorized to involve the stabilization of a subset of the active synapses after an initial overproduction of synapses triggered by a strong learning experience (Doyle et al., 1992b;

Table 1
Effect of intrinsic stress on subsequent NCAM and PSA-NCAM expression.

Learning task	Short-term effects (0–6 h)	Medium-term effects (8–12 h)	Long-term effects (24 h)
Passive avoidance	↓ NCAM (DG)	↑ PSA-NCAM (HC, DG, PFC)	↑ PSA-NCAM (HC)
Morris water maze	= NCAM (HC, PFC, FC)	↑ PSA-NCAM (DG, EC)	↑ NCAM (HC) ↑ PSA-NCAM (HC)
Contextual fear conditioning			
Moderate shock intensity (0.4 mA)	= PSA-NCAM (DG)	↓ NCAM (HC) ↑ PSA-NCAM (DG)	= NCAM (HC) ↑ PSA-NCAM (DG)
High shock intensity (1 mA)	= PSA-NCAM (DG)	↓ NCAM (HC) ↓ PSA-NCAM (HC, DG)	↑ NCAM (HC) ↑ PSA-NCAM (DG)

Summary of alterations in NCAM and PSA-NCAM expression following stressful learning conditions observed in rodent studies including stressful learning situations (for more details see main text). Abbreviations: HC, hippocampus; DG, dentate gyrus; EC, entorhinal cortex; PFC, prefrontal cortex; FC, frontal cortex.
↑, increased expression; ↓, reduced expression; =, no changes.

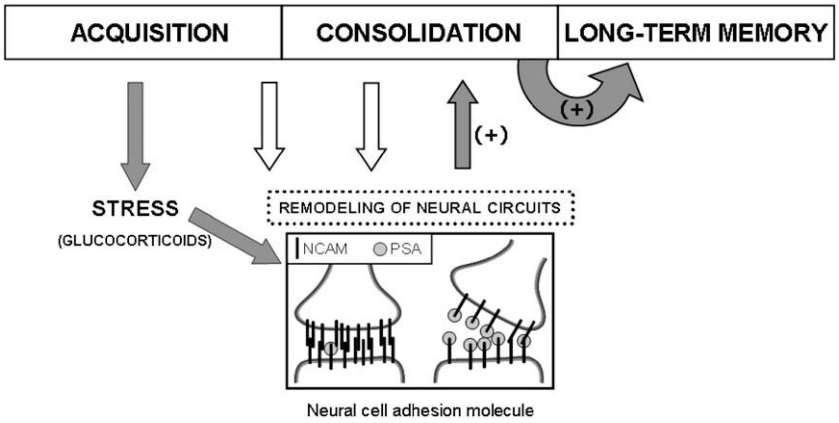

Fig. 1. Cartoon depicting the participation of intrinsic stress (and glucocorticoids) elicited by the training task (learning, acquisition) on the activation of synaptic NCAM and PSA-NCAM processes during the consolidation period, as a mechanism that facilitates the transfer of the acquired information into a long-term memory. White arrows are related to the neural remodeling mechanisms involved in long-term memory formation and that occur during acquisition and consolidation phases. Dark arrows are related to the contribution of stress to the neurobiology of long-term memory. Stress (including a glucocorticoid action), in synergy with processes initiated by training, transiently activates the expression of NCAM and PSA-NCAM in memory-associated brain regions (notably the hippocampus) and thereby facilitates the establishment of long-term memories.

Murphy & Regan, 1998). In agreement with such idea is the fact that a massed water maze training was not paralleled by changes in NCAM mRNA in the hippocampus when analyzed immediately after training (Venero et al., 2004), but was followed by increased synaptic NCAM expression in the hippocampus when the analysis was performed 24 h after water maze training (Venero et al., 2006). Such upregulation of synaptic NCAM was mainly due to isoform-specific increase of NCAM-140 and NCAM-120 expression. NCAM-120 is expressed in glial cells. Even though rising evidence supports a role for astrocytes in synaptic plasticity and potentially in learning (Schummers, Yu, & Sur, 2008), a putative role for NCAM-120 in such processes has not yet been explored. However, substantial evidence supports a role for NCAM-140 (expressed both in neurons and glia) in plasticity and intracellular signaling (for a review, see Ditlevsen, Povlsen, Berezin, & Bock, 2008). For example, a constitutive association has been found between NCAM-140 and Fyn (a member of the Src family of non-receptor tyrosine kinases highly expressed in neural tissue) (Ditlevsen et al., 2008). Interestingly, Fyn activation leads to recruitment and activation of the focal adhesion kinase (FAK), which is another non-receptor tyrosine kinase. FAK has been shown to be coimmunoprecipitated with NCAM and Fyn in neurons and to be phosphorylated upon NCAM stimulation (Beggs, Baragona, Hemperly, & Maness, 1997). Prybylowski et al. (2005) implicated Fyn in regulating internalization and synaptic localization of NR2B-containing NMDA receptors. The association of NCAM-140 with Fyn and the activation of Fyn followed by recruitment and activation of FAK upon NCAM stimulation represent a way in which NCAM-140 itself can activate intracellular signaling pathways leading to neurite outgrowth on NCAM stimulation. Interestingly, the importance of NCAM-140 in memory formation is further supported by a study (Touyarot, Venero, & Sandi, 2004) showing that NCAM-140 was the NCAM isoform specifically reduced in rats submitted to a chronic stress procedure that simultaneously impaired spatial memory.

4. Glucocorticoids, as mediators of intrinsic stress effects on learning, and NCAM

As stated above, glucocorticoids interacting with glucocorticoid receptors have been implicated as key mediators of the effects of stressful learning on long-term memory facilitation by modulation of the consolidation processes. Systemic injection of corticosterone (at a dose that mimics plasma steroid concentrations produced by substantial stress, and were shown to facilitate certain types of memory when injected immediately after submitting animals to weak training) induced an increased expression of NCAM 8 and 24 h post-injection in the frontal cortex, whereas no changes were found in the hippocampus and the hypothalamus (Sandi & Loscertales, 1999). Given that hippocampal cells present a high density of mineralocorticoid and glucocorticoid receptors and hippocampal dependent learning is facilitated by post-training corticosterone administration, it is striking that no changes in NCAM expression were found in the hippocampus. However, this might indicate that glucocorticoids need to synergize with training-induced activity and biochemical cascades in relevant neural pathways within the hippocampus (and probably other brain regions). Experiments involving weak training protocols and corticosterone injections

or, alternatively, strong training conditions and glucocorticoid synthesis inhibitors or glucocorticoid receptor antagonists, would be needed to establish whether stressful learning-induced modulations of hippocampal NCAM expression can be causally modulated by manipulating glucocorticoid actions.

Interestingly, recent work implicated the MAPK signaling cascade in the facilitation of contextual fear conditioning induced by post-training intrahippocampal corticosterone administration (Revest et al., 2005). This is relevant in the context of some of the mechanisms of action linked to NCAM signaling cascades. It has been shown *in vitro* that the FGL NCAM mimetic peptide, which potentiates both contextual fear conditioning and water maze training when given immediately after training (Cambon et al., 2004), activates – beside other signaling cascades – the MAPK intracellular signaling pathway (Neiiendam et al., 2004). Thus, NCAM might be implicated in the glucocorticoid receptor-mediated activation of the MAPK cascade occurring during memory consolidation for (hippocampus-dependent) stressful learning experiences. Gene expression studies have confirmed NCAM among the corticosterone-responsive hippocampal genes that are regulated through a GR action (Datson, van der Perk, de Kloet, & Vreugdenhil, 2001).

5. Extrinsic stress and NCAM

Extrinsic stress is stress that occurs 'outside the context' of the learning task (de Kloet et al., 1999; Sandi & Pinelo-Nava, 2007). Contrary to the facilitating influence of learning-induced activation of the stress system (intrinsic stress) on memory consolidation, acute exposure to extrinsic stress can have beneficial or deleterious effects on learning and memory, depending on the type of learning and the timing at which the stressor is applied with regard to the memory phase. In our recent literature review (Sandi & Pinelo-Nava, 2007) we reasoned two main conclusions from available data in the literature as to how acute extrinsic stress affects learning: (1) pre-training stress tends to facilitate Pavlovian conditioning processes, while (2) stress given before retention tests for explicit-like types or information (e.g., spatial learning) tends to interfere with the memory retrieval. We will now expand briefly on the work that led to these conclusions and then question the available evidence regarding the involvement of NCAM on these stress regulatory processes.

As to the effects of acute extrinsic stress on the acquisition of Pavlovian conditioning, substantial work has been performed with the eyeblink conditioning (Shors, 2004). In this task, the animal learns to associate a conditioned stimulus (CS; frequently a tone) with an unconditioned stimulus (US; frequently a periorbital shock to the eyelid). By itself, the US leads to an eye blinking (unconditioned response, CR). By exposing rats to frequent pairing of the tone and the shock, they learn over time to associate both stimuli and to respond to the tone by eye blinking, before or even in the absence of the shock. Pre-training application of an acute inescapable stressor consisting on a coupling of restraint and intermittent tail-shocks has been repeatedly shown to enhance this type of associative learning (Servatius & Shors, 1994; Shors & Servatius, 1997; Shors, Weiss, & Thompson, 1992). Learning is enhanced if training occurs immediately after the stressor or even 24 h later suggesting that its effects are rapid and long lasting. Beside the facilitating effect of pre-training stress exposure on classical eyeblink conditioning, the acquisition of fear conditioning has also been shown to be highly susceptible by prior stress exposure. For instance, acute exposure to a single restrain stress session facilitated subsequent auditory and contextual fear conditioning in rats and mice (Cordero et al., 2005; Radulovic, Ruhmann, Liepold, & Spiess, 1999; Rodriguez Manzanares, Isoardi, Carrer, & Molina, 2005).

The molecular mechanisms governing this facilitation are unclear and evidence linking this particular type of stressors with the expression of NCAM or PSA-NCAM is missing. However, circumstantial evidence suggests their potential implication and we will expose it here without implying that any direct proof for a link between NCAM and eyeblink conditioning actually exist. Thus, eyeblink conditioning increases neuronal activity and spine density in hippocampal CA1 region (Berger, Rinaldi, Weisz, & Thompson, 1983; Leuner, Falduto, & Shors, 2003; McEchron & Disterhoft, 1999). Interestingly, the same acute extrinsic stress that facilitates eyeblink conditioning is able, by itself, of increasing both hippocampal dendritic spine density (Shors, Chua, & Falduto, 2001) and excitability of CA1 pyramidal cells (Weiss, Sametsky, Sasse, Spiess, & Disterhoft, 2005) in male rodents. Furthermore, rapid spinogenesis of pyramidal neurons is induced by a single application of the synthetic glucocorticoid dexamethasone (Komatsuzaki et al., 2005) and NCAM and PSA-NCAM are known to be critically involved in regulating spinogenesis and synapatogenesis (Dityatev et al., 2004; Muller et al., in press), as well as synaptic activity (Bukalo et al., 2004; Cremer et al., 1998; Lüthi et al., 1994; Muller et al., 1996; Ronn et al., 1995; Senkov et al., 2006). Moreover, the basolateral amygdala (BLA) has been implicated in the facilitation of eyeblink conditioning induced by prior stress (Shors & Mathew, 1998; Waddell, Bangasser, & Shors, 2008) and recent evidence indicates that PSA-NCAM in this amygdaloid nucleus is highly responsive to different stress schedules (Cordero et al., 2005; Markram et al., 2007b). However, the potential implication of PSA-NCAM (and NCAM) in the amygdala on stress effects on conditioning processes still remains to be tested.

More information is available with regards to the regulation of NCAM under conditions related to disrupting effects of extrinsic stress on the retrieval of previously acquired information. Such disruptive effects have been shown to occur when stress is applied 30 min before a retention session, 24 h after training animals in the water maze (de Quervain, Roozendaal, & McGaugh, 1998) and when it is applied during the 30 min before testing in a radial arm water maze under a protocol in which learning was applied on the same day just before both, stress and retention testing (Diamond, Park, Heman, & Rose, 1999; Sandi et al., 2005; Woodson, Macintosh, Fleshner, & Diamond, 2003). Glucocorticoids were implicated in the impairing effect of stress, with increasing corticosterone levels being necessary and sufficient (though interacting with noradrenergic mechanisms in the basolateral amygdala) to impair retrieval when animals were tested 24 h after training (de Quervain et al., 1998; Roozendaal, Griffith, Buranday, De Quervain, & McGaugh, 2003; Roozendaal, Hahn, Nathan, de Quervain, & McGaugh, 2004). Glucocorticoids have also been implicated, although by themselves shown not to be sufficient, to block retrieval when the effects of stress on retrieval were examined immediately after having trained rats in the radial arm water maze (Woodson et al., 2003).

A modulation in hippocampal NCAM expression has been associated with a predator stress induced deficit in the retrieval of spatial information acquired in the radial arm water maze (Sandi et al., 2005). Specifically, a 30 min predator stress exposure (cat exposure) immediately after training induced a marked suppression of the synaptic NCAM-180 isoform in the hippocampus. Moreover, predator stress also induced a more global reduction of NCAM levels in the prefrontal cortex, but had no effect on NCAM levels in the amygdala or cerebellum (Sandi et al., 2005). However, one should be cautious as to the conclusions that can be extracted about the potential functional meaning of such regulation. Even though in this study, cat exposure took place throughout a 30-min period between the acquisition and retrieval phases (testing took place 30 min post-training), a subsequent paper showed that the same stress manipulation (i.e., cat exposure given immediately after

training), in addition to short-term memory, it impaired as well short-term memory processes involved in memory consolidation and retrieval (Park, Zoladz, Conrad, Fleshner, & Diamond, 2008). Therefore, at this stage, it is not possible to ascertain whether NCAM reductions observed immediately after predator stress would be linked to stress-induced impairment of consolidation, retrieval or to both processes. In fact, given the well known involvement of NCAM in long-term memory formation (see above), it is plausible that the strong reduction of NCAM levels found in the hippocampus shortly after predator stress contributes, at least, to impaired long-term consolidation of spatial memory. Whatever type of 'cognitive' processes is involved, it is interesting to note that a recent work showed that an antidepressant treatment resulting in upregulation of NCAM expression was protective against the negative effect of predator stress on spatial memory retrieval (Conboy et al., 2008).

An important issue to address is the promptness at which NCAM changes took place after exposure to predator stress. Whereas processes leading to enhanced NCAM expression would require a time-lapse of hours to allow for protein synthesis to take place, the rapid time course of NCAM synaptic downregulation observed after cat exposure can be sustained by fast mechanisms, including its internalization from the cellular membrane followed by either degradation or by redistribution among cellular compartments (Bailey, Chen, Keller, & Kandel, 1992; Foley et al., 2000; Mayford, Barzilai, Keller, Schacher, & Kandel, 1992), and/or its extracellular release (Fazeli, Breen, Errington, & Bliss, 1994). Rapid NCAM release and degradation have been reported to be induced by stimulation of glutamatergic receptors (Endo et al., 1999; Hoffman, Larson, Bahr, & Lynch, 1998) and the induction of hippocampal LTP (Fazeli et al., 1994).

The relevance of these findings for the understanding of how extrinsic stress can interfere with spatial memory retrieval can only be indirectly discussed since so far no intervention has just addressed the effects of interfering with NCAM or PSA-NCAM function on retrieval of information. Most of the evidence comes from work done with C3d, the mimetic peptide that disrupts NCAM function related to homophilic adhesion. Following intracerebroventricular injection, C3d was able to inhibit long-term retrieval of previously acquired information while having no effect on the initial phases of spatial learning in the water maze (Venero et al., 2006). However, the fact that the peptide had been injected pretraining does not allow excluding potential effects on memory consolidation. In fact, when injected during the post-training period, the C3d peptide was also shown to interfere with the eventual retention of contextual fear conditioning (Cambon et al., 2003) and passive avoidance learning (Foley et al., 2000). These findings strongly support a key role of hippocampal NCAM downregulation in the impairing effects induced by acute extrinsic stress on the consolidation and/or retrieval of spatial information, but they do not allow to draw any conclusion as to whether or not NCAM interference would disrupt recall or not. On the other hand, no evidence is currently available as to an implication of PSA-NCAM on these processes. However, Pham, Nacher, Hof, and McEwen (2003) showed that a single acute restraint session did not modify PSA-NCAM levels in the hippocampal dentate gyrus.

6. Conclusions

Drawing from a vast pool of research, we have analyzed here the literature related to the neurobiological contribution of NCAM and PSA-NCAM on learning and memory processes under situations involving acute intrinsic or extrinsic stress. The reviewed evidence leads us to suggest that NCAM and PSA-NCAM are involved in the memory facilitation induced by intrinsic stress (Fig. 1). As for extrinsic stress, further work is needed before any conclusion can be drawn about a potential role of this adhesion molecule. Whereas data relating NCAM to acute stress-induced facilitation of conditioning processes is still lacking, the experimental designs followed so far to investigate NCAM contribution to extrinsic stress effects on retrieval processes do not allow distinguishing between its potential associations with retrieval and/or consolidation processes. In any case, what this latter line of research indicates is that extrinsic stress applied after training and impairing recall (including to impaired short-term memory, retrieval and consolidation of long-term memory) would have the converse effect to that observed under intrinsic stress conditions leading to facilitated memory; i.e., the inhibition of NCAM synaptic expression in neural pathways critically involved in information processing and recall, such as the hippocampus and prefrontal cortex. In summary, we propose that NCAM and PSA-NCAM are important regulators of the effects of acute intrinsic stress on memory consolidation. Furthermore, this review highlights NCAM as one of the molecules potentially involved in some of the bidirectional effects of stress on memory processes, with its enhanced synaptic expression involved in facilitating stress actions while its reduced expression being related to impairing effects of stress on mnemonic processes.

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