SA1

New observations on the role of αCaMKII in LTP

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There is abundant evidence that the calcium/calmodulin-dependent protein kinase αCaMKII plays a critical role in the genesis of LTP in the Schaffer-collateral projection to hippocampal CA1 pyramidal cells. Specific inhibitors of the enzyme prevent the development of LTP (Malenka *et al.* 1989), and genetically engineered mice with a targeted deletion of the gene encoding αCaMKII fail to exhibit LTP in area CA1 (Silva *et al.* 1992). In a widely discussed model of the mechanism by which the enzyme affects the processes underlying LTP, a rise in intracellular Ca^{2+} caused by the LTP-inducing stimulation leads to activation of the enzyme and autophosphorylation on threonine 286 (Lisman *et al.* 2002). Phosphorylation on this residue in the multimeric enzyme results in autonomous activation, a state in which the enzyme no longer requires Ca^{2+}–calmodulin for activity. The persistence of autonomous activity, and resulting phosphorylation of substrates, including AMPA receptor subunits, has been suggested to contribute to the maintenance of LTP (Lisman *et al.* 2002).

We have examined levels of autonomous activity in hippocampal slices in which LTP was induced either by titanic stimulation, or by exposure to the K^+ channel blocker tetraethylammonium (TEA). In contrast to an earlier report of a persistent increase in autonomous activity following tetanus-induced LTP (Fukunaga *et al.* 1993), we did not observe a sustained increase in autonomous activity in either case. However, TEA-induced LTP led to a persistent increase in Thr286 phosphorylation, as observed by others for tetanus-induced LTP. Moreover, in animals with a threonine to alanine point mutation at residue 286, TEA failed to induce LTP, as previously demonstrated for tetanus-induced LTP (Giese *et al.* 1998). Thus, phosphorylation at Thr286 rather than persistent autonomous activation of the enzyme is the critical factor determining whether or not LTP is produced. In a further series of experiments we monitored LTP *in vivo* in the T286A mutant, and find that while LTP in area CA1 is absent in the mutant, it is relatively unaffected in the dentate gyrus. Thus, the current model for the involvement of αCaMKII in LTP requires modification in area CA1, and cannot account for LTP in the dentate gyrus.

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SA2

Signalling via MAPK to zif268 in LTP and memory

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The formation of long-term memory is thought to depend on long-lasting changes in synaptic efficacy and the reorganisation of neuronal networks. Experimental evidence suggests that the mechanisms underlying these processes engage the genetic program of neurons and *de novo* synthesis of proteins. To date, the prevailing model for cellular consolidation underlying the laying down of memory suggests that synapse-to-nuclear signalling and transcriptional regulation of genes are required to maintain long-lasting synaptic modification in neural networks activated during learning. Although the molecular events coupling cell activation to gene transcription have not been entirely resolved, two important steps in this process appear to be critical: the activation of protein kinases and of constitutively expressed transcription factors and, shortly after, the expression of a class of inducible immediate early genes (IEGs) encoding regulatory transcription factors that interact with promoter regulatory elements of a host of downstream effector genes. Zif268, also known as Krox24, Egr1 or NGFI-A, is one such IEG encoding a zinc finger transcription factor of the Egr family, which has been implicated in synaptic plasticity and memory consolidation.

Here, we first describe experiments showing that the ERK family of mitogen-activated protein kinase (MAPK) is critically involved in LTP-induced regulation of zif268 *in vivo*. In these experiments, we found that LTP in the dentate gyrus leads to rapid phosphorylation of MAPK/ERK and subsequent co-ordinated phosphorylation of the two downstream transcription factors, CREB and Elk-1. Inhibition of MAPK/ERK phosphorylation by a MEK inhibitor was shown to block phosphorylation of both CREB and Elk-1, and also to block LTP-dependent transcriptional activation of zif268 in dentate granule cells, resulting in a rapidly decaying LTP. These results show that MAPK/ERK controls zif268 expression in LTP and that this is mediated by two parallel and possibly co-operating signalling pathways, one targeting CRE-mediated transcription via CREB and the second targeting SRE-mediated transcription via Elk-1 (Davis *et al.* 2000). Next, in collaboration with Tim Bliss and his colleagues we investigated the role of zif268 in LTP and learning using mutant mice in which the zif268 gene is inactivated (Jones *et al.* 2001). In these mice, basal synaptic transmission and forms of short-term plasticity were normal in the dentate gyrus; however, LTP, which was normal for the first hour, was not maintained over 24 h in awake zif268 mutant mice, showing that the zif268 gene is necessary for the expression of the late phases of LTP. At the behavioural level, we found that long-term memory in zif268 mutant mice, but not short-term memory, is severely impaired in several tasks including social transmission of food preference, conditioned taste aversion and spatial navigation in the water-maze. We then explored the role of MAPK/ERK, CREB and zif268 in recognition memory, using a task based on the spontaneous preference of rodents for novelty and their ability to remember previously encountered objects. Our results show that blocking MAPK/ERK activation by inhibiting the upstream kinase MEK, turning CREB function off in transgenic mice, or inactivating zif268 in mutant mice, all resulted in a similar deficit in long-term, but not short-term, recognition memory (Bozon *et al.* 2003). Finally, we will describe experiments showing that this signalling cascade is also required

for reconsolidation of recognition memory after retrieval (Kelly *et al.* 2003). Together with a wealth of experimental data showing that each of these molecules plays important roles in mediating long-term changes in neuronal function, our results are consistent with the view that MAPK/ERK activation and the subsequent transcriptional regulation of the IEG zif268 is an important signalling cascade recruited during, and required for, the formation of long-term memory.

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SA3

BDNF as a trigger for synaptic consolidation

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Neurotrophic factors are important regulators of neuronal development and survival, yet the functions of neurotrophins in the adult brain are still little understood. Recent evidence suggests that one of the neurotrophins, brain-derived neurotrophic factor (BDNF), plays a critical role in activity-dependent synaptic plasticity. We have examined the effects of local BDNF infusion on synaptic efficacy at medial perforant path granule cell synapses in the dentate gyrus of anesthetized rats.

Infusion of BDNF (2 μg in 2 μl, 25 min) into the dentate gyrus led to a long-term potentiation of synaptic transmission termed BDNF-LTP. BDNF-LTP requires activation of extracellular signal-regulated kinase (ERK), and is coupled to ERK-dependent phosphorylation of CREB and upregulation of the immediate early gene Arc (activity-dependent cytoskeleton-associated protein). Arc mRNA is rapidly induced in postsynaptic granule cells bodies and delivered to granule cell dendrites. Local infusion of MEK inhibitors (PD98059, U0126) or the RNA synthesis inhibitor actinomycin D blocked BDNF-LTP and the associated upregulation of Arc. Defining a rapid time window of activation, these inhibitors had no effect on established BNDF-LTP. Zif268, another early gene required for generation of transcription-dependent LTP, was not induced. The functional role of BDNF-LTP was assessed in occlusion experiments with classical high-frequency stimulation-induced LTP (HFS-LTP). HFS-LTP was induced and BDNF was infused at time points corresponding to early phase (1 h) and late phase (4 h) HFS-LTP. BDNF applied during the early phase led to normal BDNF-LTP, indicating lack of occlusion. In contrast, BDNF had no effects when it was applied during late, protein synthesis-dependent LTP, indicating occlusion. Taken together, the results suggest that BDNF acts as a synaptic consolidation factor, effectively governing the switch from transcription-independent to transcription-dependent LTP. Further work shows that BDNF also modulates translation control processes. α-CaMKII mRNA, which is constitutively expressed in granule cell dendrites in adult rats, is an attractive target for regulation. For example, in isolated synaptodendrosomes, BDNF treatment induces a rapid (3–5 min) increase in CaMKII protein levels paralleled by an increase in CaMKII activity. In awake rats, high-frequency stimulation of the perforant pathway induces rapid delivery of pre-existing CaMKII mRNA to synapses coupled to enhanced expression of CaMKII protein.

In conclusion current evidence from our laboratory suggests that BDNF regulates synaptic consolidation through dual regulation of transcription and translation. We are currently examining the hypothesis that Arc, a dendritic mRNA species, is causally involved in BDNF-induced LTP.

SA4

The age-related increase in hippocampal concentration of the proinflammatory cytokine, interleukin-1β, significantly contributes to the impairment in long-term potentiation in perforant path-granule cell synapses

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Among the several changes which accompany ageing is a compromise in synaptic function, one manifestation of which is an impairment in long-term potentiation (LTP). Several cellular and molecular changes occur in the aged brain which are likely to contribute to this impairment; it has been shown recently that there is evidence of tissue stress in the aged hippocampus and the evidence suggests that this may be a pivotal factor in causing the age-related impairment in LTP. Thus activities of the stress-activated protein kinases, c-jun N-terminal kinase (JNK) and p38 are significantly increased in the hippocampus of the aged, compared with the young, rat. The evidence suggests that these changes are a consequence of increased hippocampal concentration of the proinflammatory cytokine, interleukin-1β (IL-1β), coupled with increased expression of IL-1 receptor type I (IL-1RI) and increased activation of IL-1 receptor associated kinase (IRAK). The age-related increase in activation of JNK and p38, which lead to activation of the transcription factors, c-jun and nuclear factor κB (NFκB), respectively, ultimately induces cellular changes which suggest that apoptotic cell death occurs in the aged brain. Thus cytochrome c translocation, caspase-3 activation and cleavage of poly ADP ribose polymerase (PARP) are enhanced in hippocampal tissue prepared from aged, compared with young, rats; consistently TUNEL staining was also shown to be enhanced in acutely dissociated cell prepared from aged, compared with young, rats.

The key role of IL-1β and the signalling events induced by IL-1 receptor activation in stimulating activities of JNK and p38 and in inducing cell death has been underscored in recent studies; thus several manoeuvres which reduce the age-related increase in IL-1β concentration or IL-1β-induced signalling inhibit activation of JNK and p38 and resultant apoptotic changes. These manoeuvres include treatment of rats with the polyunsaturated fatty acid, eicosapentaneoic acid (EPA) or phosphatidyl serine-bearing liposomes, both of which block the age-related increase in IL-1β concentration. Both treatment schedules inhibit the age-related impairment in LTP. Increased activation of JNK and p38 in hippocampus of aged rats is coupled with decreased activation of extracellular signal-regulated protein kinase (ERK) and the transcription factor, cAMP response element-binding protein (CREB), and the combined importance of these age-related changes has been emphasized in recent studies. It has emerged that a proportion of aged rats sustain LTP; the evidence suggests that about 25 % of 22 month-old animals sustain LTP. In a recent study, hippocampal tissue was prepared from aged rats which did and did not sustain LTP. Analysis revealed that IL-1β concentration, JNK activation and JNK translocation to the nucleus were significantly enhanced in hippocampal tissue prepared from aged rats which did not sustain LTP, compared with aged rats which sustained LTP and young rats. The data indicated that there was an indirect correlation between activation of JNK and activation of ERK, such that ERK activation was significantly reduced in hippocampus of aged rats which failed to sustain LTP, compared

with young rats and aged rats which sustained LTP. These data will be discussed in the light of other findings which indicate that decreased hippocampal concentrations of anti-inflammatory cytokines, IL-4 and IL-10, and downregulation of signalling events triggered by IL-10 and IL-4 receptor activation, together with upregulation of IL-1β and IL-1β-triggered signalling, combine to lead to the age-related impairment in LTP.

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SA5

Redox signalling in hippocampal LTP and memory function

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Historically, reactive oxygen species (ROS) have been viewed as toxic molecules that cause oxidative stress. However, this view has been challenged by studies from a number of laboratories in recent years. It is becoming increasingly clear that many cell types, including neurons, employ ROS as cellular messengers to modulate signal transduction pathways that are necessary for normal physiological processes. Consistent with this notion, in previously published studies several laboratories, including ours, have shown that ROS are critical for hippocampal long-term potentiation (LTP) in area CA1. In addition, we, and others have shown that LTP and hippocampus-dependent memory are impaired in transgenic mice that overexpress either cytoplasmic superoxide dismutase (SOD-1) or extracellular superoxide dismutase (EC-SOD). Taken together, these findings suggest that, in contrast to the historical view of ROS as toxic molecules, ROS can act as signalling molecules that are critical for normal synaptic plasticity and memory function.

If ROS are critical for hippocampal synaptic plasticity and hippocampus-dependent memory, then what signalling cascades are impacted by ROS? One candidate is the extracellular signal-regulated kinase (ERK) cascade, which has been shown to be both activated during and necessary for NMDA receptor-dependent LTP. In addition, incubation of hippocampal slices with ROS has been shown to result in ERK activation. Finally, NMDA receptor activation has been shown to result in the production of ROS. Therefore, we hypothesized that NMDA receptor-dependent activation of ERK requires ROS. We have found that NMDA receptor-dependent activation of ERK in hippocampal area CA1 is blocked by both superoxide and hydrogen peroxide scavengers. The NMDA receptor-dependent activation of ERK also was blocked by NADPH oxidase inhibitors, which suggests that NADPH oxidase is the source of ROS required for ERK activation. These results are consistent with the possibility that the ERK signalling cascade is impacted by ROS during NMDA receptor-dependent LTP.

We also have begun to investigate how ROS are produced during LTP and hippocampus-dependent memory. We are currently conducting studies with gp91phox and p47phox (two of the necessary protein components of NADPH oxidase) knockout mice to determine whether NADPH oxidase is necessary for either LTP and/or hippocampus-dependent memory. In addition, we are conducting studies with transgenic mice that overexpress MnSOD (SOD-2) to determine whether mitochondrial ROS production is necessary for LTP and/or hippocampus-dependent memory. The results of these studies should provide insight into how ROS are produced during hippocampal LTP and hippocampus-dependent memory.

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SA6

Aβ-mediated depression of hippocampal synaptic plasticity: mechanism of action?

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Alzheimer's disease is a disorder leading to neurodegeneration, progressive decline in cognitive function and premature death. This disease is accompanied by the deposition of numerous senile plaques and neurofibrillary tangles in the affected brain regions. β-Amyloid peptide (Aβ), is the main constituent of these plaques. It is a 39–42 amino acid peptide derived by proteolysis of amyloid precursor protein (APP). There appears to be a correlation between amyloid load in the cortex and disease progression on a cognitive level. We have used hippocampal long-term potentiation (LTP) in the CA1, which is a cellular model of memory, to study the effects of Aβ peptides on synaptic transmission and plasticity *in vivo* and also *in vitro*.

LTP was induced by applying a series of high frequency stimuli (HFS) comprising three episodes of 10 stimuli at 200 Hz, 10 times at 30 s intervals to the Schaffer-collateral pathway. In addition to activating the NMDA-receptor system this stimulus frequency activates L-type Ca^{2+} channels that are also involved in the induction of LTP (Freir & Herron, 2003*a*). In our *in vivo* studies, Aβ peptides were applied via intracerebroventricular (I.C.V.) injection and LTP levels were compared with those obtained following injection of water vehicle. Normal LTP was recorded following injection of vehicle or Aβ [15–25]. We found that injection of the toxic fragment Aβ[25–35] either reduced (10 nmol) or abolished (100 nmol) LTP. The reverse sequence peptide Aβ [35–35] also significantly depressed LTP (Freir *et al.* 2001) while lower concentrations (1 or 10 nmol) of the endogenous peptide Aβ [1–40] significantly depressed LTP (Freir and Herron, 2003*b*)

In view of the reported increased activation of L-type Ca^{2+} channels by Aβ (Ueda *et al.* 1997), we investigated the effect of L-type channel blockers on Aβ-mediated depression of LTP *in vivo* and also *in vitro*. Aβ[25–35]was applied I.C.V. and L-type blockers via intraperitoneal injection (I.P.) *in vivo*. All agents were bath applied in experiments that utilized the hippocampal slice preparation. We found that the VDCC blockers diltiazem and verapamil caused a dose-dependent depression of LTP in both preparations. Consistent with our previous observations, Aβ [25–35] depressed LTP, but prior treatment in either preparation with verapamil resulted in a significant reversal of the depression of LTP observed in the presence of either agent alone (Freir *et al.* 2003). These results indicate that verapamil, which is a phenylalkylamine, may therefore be useful in the treatment of cognitive deficits associated with Alzheimer's disease.

Another series of experiments were performed to investigate a possible link between the depression of LTP produced by Aβ [1–40] and the α-7 nicotinic acetylcholine receptor (α-7 nAchR). The α-7-nAchR has been shown to bind Aβ-peptide with high affinity, the binding domain comprising amino acids 12–28 (Wang *et al.* 2000). We therefore investigated the effects of Aβ[12–28], in addition to an antagonist of the α-7 nAchR, methyllycaconitine (MLA) and nicotine on LTP. Aβ[12–28] had no effect on LTP, while MLA significantly depressed LTP. This suggests that activation of the α-7 nAchR is a requirement for LTP. Application of nicotine (I.P.) prior to I.C.V. injection of Aβ[1–40], however, caused a further significant depression of LTP compared to treatment with Aβ[1–40] alone. Nicotine therefore appears to enhance the deficit in LTP produced by

Aβ[1–40], indicating that nicotine may augment the depressive effects of Aβ on synaptic plasticity in Alzheimer' s disease.

Data will also be presented on our most recent study in which we have examined the effects of inhibitors of c-Jun-N-terminal kinase (JNK) on the depression of LTP mediated by Aβ[25–35](Costello & Herron, 2003), Aβ[1–40] and also on signalling down stream from JNK (Schmid *et al.* 2003).

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SA7

Synaptic plasticity and behaviour – role of aminergic mechanisms regulating LTP induction

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Artificially induced synaptic plasticity has many forms, some of which may mimic naturally occurring processes more closely than others. The sensitivity of electrically induced synaptic plasticity to behavioural conditions provides a powerful means of determining how well they model naturally occurring synaptic plasticity. Recently we have examined the role of aminergic inputs to the intact hippocampus in mediating/modulating the effects of exposure to non-stressful and stressful environments on LTP induction in the CA1 area of the rat. In particular, exposure to a non-stressful novel environment facilitated the induction of LTP via increased dopaminergic transmission (Li *et al.* 2003). In contrast, exposure to an inescapable stressful environment blocked the induction of LTP in a manner dependent on endogenous serotonergic tone (Shakesby *et al.* 2002).

Unpredicted information that triggers exploration may be of future adaptive significance and may thus gain preferential status for memory encoding. As the rodent hippocampus is particularly tuned to spatial information storage we hypothesized that if LTP-like mechanisms are involved in encoding for memory then exposure to a novel environment that triggered exploration should facilitate LTP induction. We found that freely behaving animals that explored a novel environment for the first time had a reduced threshold for LTP induction. The facilitation of LTP was observed in a narrow time window (brief novelty exposure introduced 5 min after, but not 5 min before, conditioning stimulation). Furthermore, the facilitation of LTP induction by the novel environment was dependent on endogenous dopaminergic tone. Thus, block of D1/D5 receptors with the antagonist SCH23390 prevented the facilitation of LTP by novelty in awake animals. In contrast the β-adrenoceptor antagonist propranolol and the muscarinic cholinoceptor antagonist scopoloamine were without effect. Furthermore, activation of D1/D5 receptors with the agonist SKF38393 in anaesthetized animals was sufficient to facilitate LTP induction. This effect was blocked by the membrane-permeant PKA inhibitor Rp-cAMPS. These results strongly implicate a requirement for dopamine-dependent LTP-like synaptic plasticity in hippocampal memory formation.

Stress has been reported to either facilitate or block the acquisition, consolidation and/or recall of hippocampal-dependent learning tasks depending on experimental conditions (Diamond D, this symposium). Exposure to an inescapable stressful environment that causes behavioural 'freezing' dramatically affects synaptic plasticity, blocking LTP induction and facilitating LTD induction (Xu *et al.* 1997). A wide variety of neurotransmitter and neuroendocrine systems are activated by stress that can potentially affect synaptic plasticity. Recently we have examined serotonergic mechanisms in maintaining, or overcoming, the block of LTP induction. We investigated the effects of agents that regulate endogenous 5-HT on the ability of conditioning stimulation to induce LTP in anaesthetised animals that had been placed on an inescapable elevated platform for 30 min. Tianeptine, an antidepressant agent that lowers endogenous 5-HT levels, given after the stress reversed the block of LTP induction. In non-stressed animals the stress-evoked block of LTP was mimicked by fluoxetine and fenfluramine, agents that increase extracellular 5-HT concentration. Remarkably, raising 5-HT levels with fenfluramine in stressed animals also overcame the block of LTP induction, probably by activation of 5-HT2 receptors (see B. Ryan *et al.* this meeting). These results point to a possible key role of endogenous 5-HT in mediating and overcoming the effects of inescapable stress on plasticity at glutamatergic synapses.

Exposure to a novel environment that initiates either approach or aversion has dramatic and opposite effects on the induction of LTP in the intact hippocampus. The sensitive regulation by aminergic mechanisms points to a key role for these extra-hippocampal influences on naturally occurring synaptic plasticity.

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SA8

Cognitive and physiological assessment of stress – hippocampus interactions

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Extensive research has shown that the hippocampus is involved in learning and memory. Complementary studies have focused on long-term potentiation (LTP) as a physiological model of memory. It is perhaps paradoxical that fear-provoking experiences, which typically generate strong memories of the experience, can block the induction of hippocampal LTP (Kim & Diamond, 2002). Why should an experience that produces long-lasting memories impair LTP? My presentation will provide cognitive and physiological perspectives which may help to resolve this paradox.

First, I will discuss research from my group showing that psychological stress has no effect on the induction of LTP (100 pulses in 1 s in CA1 *in vivo* and *in vitro*, but does block a low

threshold form of LTP, referred to as primed burst (PB) potentiation (induced by a total of 5 physiologically patterned pulses). This finding indicates that stress exerts an inhibitory bias on CA1 plasticity which is more readily observed in response to threshold (PB) than suprathreshold (LTP) stimulation (Diamond & Park, 2000). Second, we found that stress selectively impaired hippocampal-dependent, but not hippocampal-independent, spatial memory. Third, we have studied the relationship between corticosterone (CORT), an adrenal stress hormone, and stress effects on PB and spatial memory. There was an inverse relationship between stress-induced increases in serum cort levels and hippocampal processing, i.e. an increase in the level of CORT correlated with a reduced magnitude of PB and impaired spatial memory.

Although these findings indicate that CORT is involved in the stress-induced modulation of the hippocampus, we have also found that stress can impair spatial memory in adrenalectomized (ADX), i.e. CORT depleted, rats. Furthermore, exogenous CORT administration, alone, does not mimic the impairing effects of stress on memory. Finally, we and others have found other conditions in which there can be an elevation of CORT levels without there being an adverse effect on hippocampal-dependent memory or PB/LTP. For example, a lesion of the amygdala or administration of an antidepressant (tianeptine) can eliminate stress effects on the hippocampus without reducing stress-evoked increases in CORT levels (Kim & Diamond, 2002). Conversely, we have found that male rats exposed to an estrous female rat exhibited stress levels of CORT, but the male rats exposed to a female rat did not exhibit a spatial memory impairment. CORT, therefore, appears to be involved in the emotional modulation of hippocampal functioning, but the elevation of CORT needs to occur in conjunction with a fear-induced behavioural state to impair hippocampal processing.

These findings indicate that stress exerts a suppressive influence on hippocampal functioning. The challenge is to understand how these findings reconcile with the observation that emotional experiences can produce powerful and long-lasting memories. I will propose that the stress experience, itself, activates hippocampal storage mechanisms (i.e. stress generates endogenous LTP) via NMDA receptor activation. The stress-induced saturation of endogenous hippocampal plasticity then interferes with the induction of electrically induced PB. In summary, my presentation will offer a functional perspective to explain our findings showing that: (1) stress impairs hippocampal-dependent memory and PB, and (2) elevated serum CORT levels, in conjunction with a fear-induced behavioural state, impair hippocampal-dependent memory and plasticity.

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