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Original Research Article

Histone Methylation Befuddledness in the Infralimbic Prefrontal Cortex and Their Association with Extinction Memory

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ABSTRACT

The limited neurological understanding especially the molecular mechanism involved in fear extinction has been attributed to the need for improved animal models for the treatment of anxiety disorders. We presently hypothesized that the mechanism, how timing of fear extinction for a specific fear affect the histone methylation and their effect in retracement. Fear memory acquisition followed by extension training was given to rats for 10 minutes which deficits in the retention of extinction memory when compared to the other which went for 24 hours of extinction after fear acquisition. The first one is immediate extinction (IE) and the second is delayed extinction (DE). We analyzed that the activity of infralimbic prefrontal cortex (IL) to prelimbic cortex (PL) was decreased in IE when compared to DE and confounded with the activity and expression of c-fos in mPFC. As a confirmation we further analyzed the acetylation of histone H3/H4 and levels of CREB binding protein (CBP) which is a histone acetyltransferase (HAT) and found that this was associated with the activation of neuron and is significantly decreased in IL of IE as compared to the DE. We finally conclude that the deficits in IE is mainly due to the sustained activation of IL because of it is associated with the changes involved in histone methylation.

Key words: Fear memory, histone acetyltransferase, histone methylation, CREB binding protein, prelimbic cortex

INTRODUCTION

Post traumatic stress disorder (PTSD) a major fear related anxiety disorders is developed mainly due to the failure to extinguish traumatic memories in many persons (VanElzakker et al., 2014). These persons are mainly under the treatment therapy of exposure usually based on extinction learning followed by retention (Craske et al., 2008). Pavlovian translational model is the bench mark for researchers worked on fear related anxiety disorders (Maren, 2005, Pare et al., 2004). The model is well described the effects of conditioned stimulus (CS) and unconditioned stimulus (US) (Myers and Davis, 2007, Bouton et al., 2006, Pavlov, 1927). Now this is been taken up as a challenge by many researchers around the globe and worked to design new therapies for the effective treatment for such disorders (Muigg et al., 2008, Wessa and Flor, 2007, Rosen and Schulkin, 1998). Published reports suggests that the fear learning followed by extinction timing had a varied effect on extinction strength (Golkar et al., 2012, Huff et al., 2009, Maren and Chang, 2006, Myers et al., 2006, Norrholm et al., 2008). It was reported that in fear learning followed by extinction training results either “erasure” (Norrholm et al.,

2008) or may reduce the fear (Chang and Maren, 2009). Moreover, other reports published controversial results on fear extinction and suggest that the IE was not as effective as in the case of DE in inhibiting the return of fear this in turn to known as ‘‘immediate extinction deficit (IED)” (Maren, 2014, Stafford et al., 2013, Long and Fanselow, 2012, Archbold et al., 2010, Kim et al., 2010, Woods and Bouton, 2008). Apart from this, Chang and Maren, 2009, found that the reduction in fear observed after IE is for short time which may be via. short term habituation and not a long term extinction. From all published reports it was suggested that the altered neural activity basically in the region of amygdala and IL subregion of mPFC plays a major role in the regulation of fear (Greenberg et al., 2013) as well as memory extinction (Sotres-Bayon et al., 2006, Quirk et al., 2000). This was supported by other studies where lesions of mPFC which results the impairment to recall the memory extinction (Milad and Quirk, 2002). During fear and extinction learning the infralimbic prefrontal cortex (IL) and prelimbic prefrontal cortex (PL) subregions of the mPFC play an important role (Quirk and Mueller, 2008) and the activity of IL positively correlates to recall the memory extinction (Milad and Quirk, 2002) as well as the PL activity to the expression of fear response (Burgos-Robles et al., 2009, Likhtik et al., 2005). Histone acetyl transferases (HATs), like CREB-binding protein (CBP/p300) are involved in the acetylation of histone at Lysine residues which is significantly associated with the consolidation of memory following fear and extinction learning (Alarcon et al., 2004, Levenson et al., 2004, Sintoni et al., 2013, Stefanko et al., 2009, Levenson et al., 2004). Increased histone methylation (H4) in neurons of IL-PFC is a well documented fact in the role to the storage of fear extinction memories (Ferreira et al., 2015). Histone methylation (H3) in CA1 (field CA1 of the hippocampus) is important for contextual fear learning (Miller et al., 2008, Lubin and Sweatt, 2007). To hypothesize this we have focused to find the effect of neuronal activity in IL with association of retention of extinction memory and changed neuronal activity in the IL following IE and may lead to the deficits in retention of memory extinction.

MATERIALS AND METHODS

SUBJECTS

Rats aged 2-3 months; weight 150-200 grams were used in the study. The experiments were done as per CPCSEA guidelines (853/AC/04/CPCSEA), Govt. of India, New Delhi. All subjects were on light/dark cycle, ambient temperature and proper food and water resources and they have individual cases. Sample size was 20-22 rats animals in each group and all experiments were performed in triplets.

Behavior Apparatus

Two plexiglass identical observation chambers kept in sound proof cabinets were used for all training such as fear and extinction. The chambers were made as per standard protocols and sophistication. A speaker was mounted outside the chamber to capture the acoustic CS. The chambers are fully ventilated and have fan. First chamber is used as conditioning (Context A) and other is for extinction (Contest B).

Conditioning

The conditioning is for 7 days for at least 5 Minutes each day. Firstly the rat directly plased into the first chamber which is dark to expose the fear learning to adapt themselves for the environment in context A for at least 3 minutes to record the freezing baseline. This was then followed by 5 consecutive session and document the freezing when no movement is recorded. The 10 second exposure of CS (tone) having the intensity of 80 dB coterminous with US (shock) of 1 second having intensity of 0.70 mA. The difference between these two trials was 1 minute and the data were recorded both by software and manually.

Extinction

Context B was used for extinction training at two point scale i.e. 10 mins and 24 hours after fear learning. Before hand the

baseline freezing was recorded for all the studied groups followed by exposure to the 3 minutes extinction context by keeping the period free from tone or shock. 30 CS tone of 80 dB for 10 sec with interval of 10 sec in monitoring the freezing behavior and the data were recorded. Total 5 blocks having 30 trials i.e. 6 repetitive trials were taken for analysis with two controls one is immediate no extinction and delayed no extinction to find the correlation.

Retention test

A group containing 20 animals of these 10 was for the retention test having 24 hours of extinction training and the other 10 were sacrificed for immunohistochemistry of brain after 2 hours of extinction. In this test, the subjects were taken in 5 consecutive trials of 80 dB for 10 sec as extinction context to record the freezing score to analyze the retention of extinction learning.

Study of Brain Sub-Regions

Brains of sacrificed subjects were taken and the antibodies against each portion were used and the data were recorded as mean of positive neurons from each subject.

Tissue Sectioning

Subjects were anesthetized in both the trial blocks and perfused transcardially using normal saline followed by chilled 4.0 % paraformaldehyde (PFA). The resulted brains were then stored in 4.0 % PFA for at least 24 hours. Serial sucrose solution of 10, 20 and 30 % were used in next day to settle the brains followed by isopentane freezing at -30 ^{0} C for 30 minutes. The samples then stored in -80 ^{0} C deep freezer for immunohistochemistry.

Immunohistochemistry

Cryostat sectioning of 20 µm thickness containing mPFC coronal brain sections were collected. These sections were blocked with 1% NHS (NHS Vecta-stain Elite ABC kit, Vector Laboratories, Burlingame, CA, USA) and 0.25 % tween 20 and followed by overnight incubation with c-fos primary antibody, acetyl H3K9, acetyl H4K5 and CBP. After this the sections were incubated with the biotinylated secondary antibody for 2 hours followed by ABC complex for 2 hours at 25 ^{0} C. Finally, DAB substrate was added and the immunostained sections were then fixed mounted on clean slides. Reading of PL and IL sub regions were recorded (All reading in triplicate).

Statistical Analysis

Behavioral data has been shown as means ± standard error and the data was analyzed using three-way repeated measures ANOVA. Post hoc corrections were made by Tukey's post hoc analysis. Two-way ANOVA was used to analyze other data using online software.

RESULTS

PFC and P-CREB expression following immediate and delayed extinction

The expression of P-*CREB* was found to be higher in extinction group as compared to their control in the PL region however; the changes were non-significant between IE and DE group. Two-way ANOVA analysis for *P-CREB* expression in PL region revealed a significant main effect of extinction condition (extinction vs. no Extinction) [$F(3, 26) = 163.3$, $P < 0.0001$], However in IL, the expression of *P-CREB* was significantly higher in DE group as compared with the IE group and delayed no extinction and this was confirmed by two way ANOVA analysis [$F(3, 26) = 139.0$, $P < 0.0001$]. Extinction time (IE vs. DE) [$F(3, 26) = 5.820$, $P < 0.0001$] as well as extinction condition and extinction time interaction [$F(3, 26) = 176.0$, $P < 0.0001$]. Or we may say that the two sub regions of Amygdala responded differentially to respective two extinction conditions. This differential expression of *P-CREB* exemplifying the activity in the PL and LA in the IE and DE group which may be responsible for the deficit in the retention of Extinction memory as observed after IE (Figure 1).

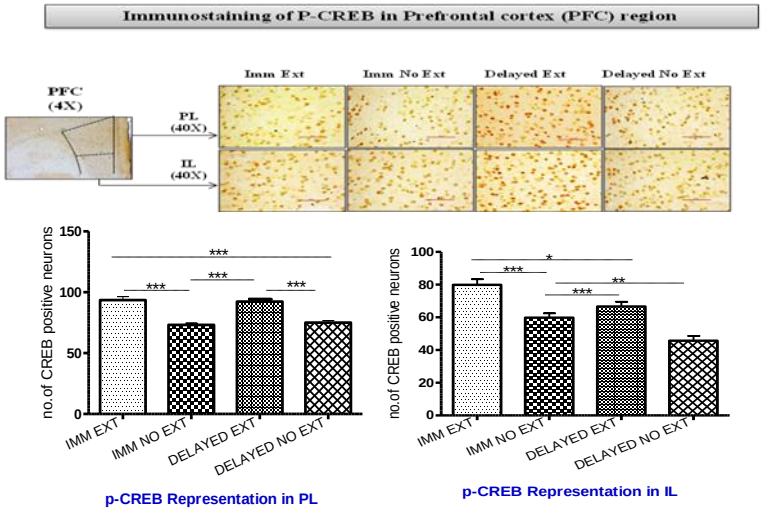

Figure 1. The *expression* of P-CREB in PFC following IE and DE learning: The *expression* of p-*CREB* was increased in the PL and IL of both IE and DE when compared to their respective controls. While, the expression of p-*CREB* was significantly increased in PL of DE as compared IE.

CREB expression following immediate and delayed extinction

The CREB expression is quite similar to P-CREB and higher in extinction groups when compared to their control however, no significant changes were observed between IE and DE groups in PL region. Two-way ANOVA analysis for CREB expression in PL region showed significant association [F (3, 26) =83.19, P < 0.0001] but no effect of extinction time in IL of IE vs. DE [F (3, 26) =191.3, P < 0.0001]. Moreover in IL, significant increment in CREB expression was observed in DE. The data further supported by using two way ANOVA analysis that explains the same significant association [F (3, 26) =5.565, P < 0.0001] extinction time [F (3, 26) =9.50, P < 0.0001]. Expression of CREB also seems to be highly associated with neuronal activity in the IL and PL following IE and DE. We further analyzed that whether the increased CREB levels in these subregions culminated in methylation of H3 and H4 which are being studies and suggest that the methylation of Histone at various lysine residues to be associated with increased gene expression required for synaptic activity and memory consolidation (Figure 2).

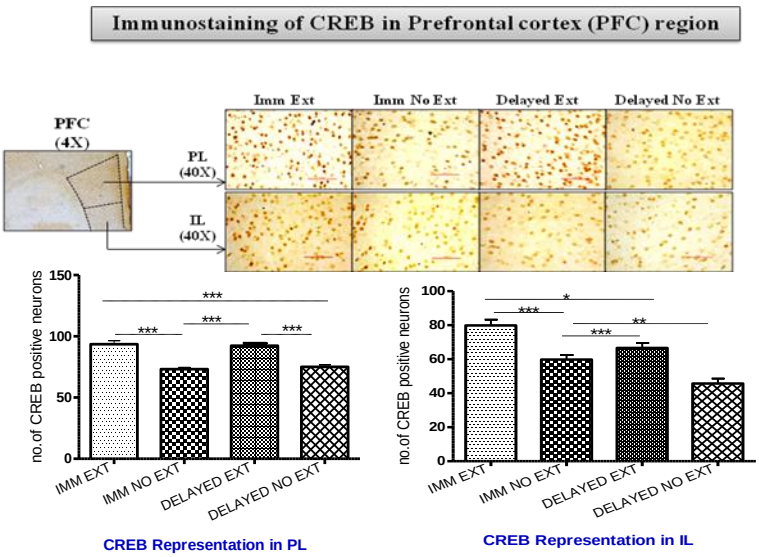

Figure 2. The *expression* of CREB in PFC following IE and DE learning: The *expression* of *CREB* was increased in the PL and IL of both IE and DE when compared to their respective controls. While, the expression of *CREB* was significantly increased in PL of DE as compared IE.

ARC expression following immediate and delayed extinction

The same were observed in this i.e. the expression was higher in extinction groups however no significant association were observed between IE and DE in PL region. The same two-way ANOVA analysis for CREB expression in PL region revealed significant association with extinction condition [F (3, 26) =131.7, P < 0.0001] but no effect of extinction time (IE vs. DE) and condition with time interaction. However in IL, there was a significant increment in gene expression of CREB when observed in DE as compared with IE and delayed no extinction group as supported by two way ANOVA analysis [F (3, 26) =310.6, P < 0.0001]. Expression of ARC seems to be highly associated with neuronal activity in the PL and IL following IE and DE. We further want to clear whether the increased ARC levels in these regions were related to the methylation of H3 and H4, suggesting methylation of Histone at various lysine residues which may be associated with increased gene expression (Figure 3).

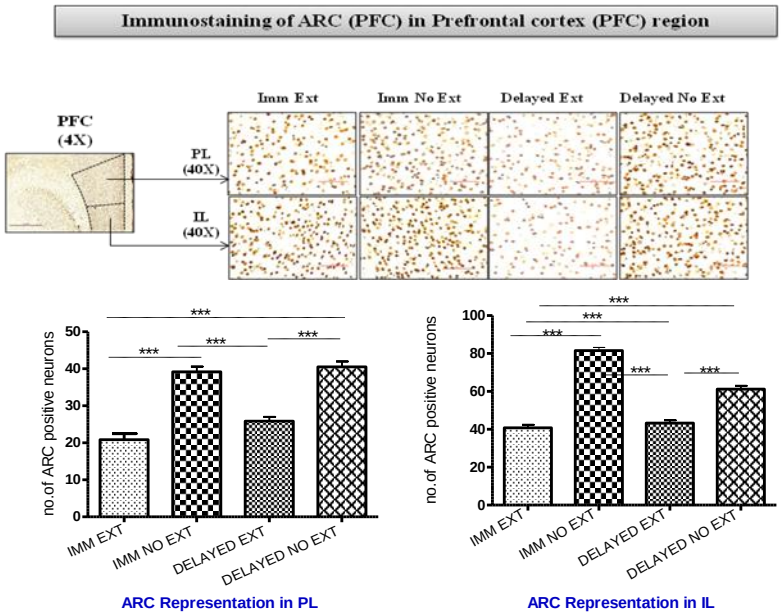

Figure 3. The *expression* of ARC in PFC following IE and DE learning: The number of ARC + ve neurons was higher in PL and IL of both IE ad DE. While, the numbers of ARC + ve neurons was significantly increased in IL of the IE as compared IE in PL.

Histone methylation following immediate and delayed extinction

We further moved to looked at histone methylation in the PL and IL following IE and DE. We gauged the levels of methyl H3 at lysine residue 9 (K9) and methyl H4 at lysine residue 5 (K5) in PL and IL following two extinctions. Expression of methyl H3K9 in LA region showed that there was no such significant association between IE and DE however, IE and DE has a decreased level of methyl H3K9 positive neurons as compared to immediate no extinction and delayed no extinction group. Two-way ANOVA analysis confirm the result [F (3, 26) =148.4, P < 0.0001]. Moreover, the effect of extinction time (IE vs. DE) [F (3, 26) = 16.48, P < 0.0001]. While in PL region, the expression of H3K9 was significantly decreased in DE using two-way ANOVA analysis of IL [F (3, 26) =172.6, P < 0.0001] and showed significant association [F (3, 26) =96.6, P < 0.0001] and extinction time (IE vs. DE) [F (3, 26) = 45.8, P < 0.0001]. These changes in the H3 methylation were definitely linked to the neuronal activity i.e., the ARC, CREB, p-CREB in a region-specific manner; similar to the H3K9 me2, the IE and DE exhibited decreased level of

H3K9 expression. While we compared to their respective control groups in IL region but no such significant association was observed between IE and DE. The result was further confirmed by two-way ANOVA analysis. However, no significant association was also observed for Extinction time (IE vs. DE) [F (3, 26) = 45.8, P < 0.0001] (Figure 4).

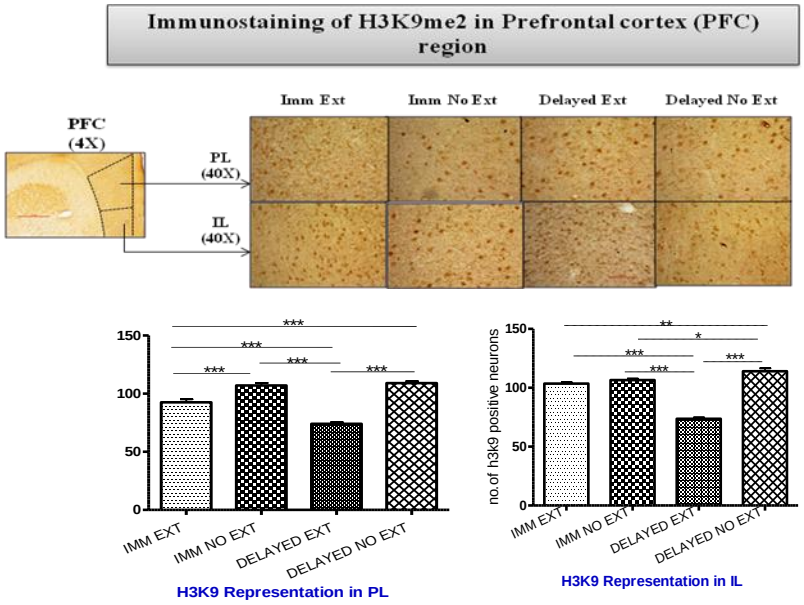

Figure 4. The expression of methyl H3k9 me2 in PFC following IE and DE learning: Histone H3 methylation at 9th residue of lysine was found to be decreased in both IE and DE in both PL and IL. DE exhibited highly significant decrease in number of Methyl H3K9 + ve nuclei in PL and IL as compared to their respective controls.

DISCUSSION

The present report depicts that the effect of IE and DE extinction on retention of extinction memory as well as the neuronal activation and histone methylation in mPFC. A great loss in the retention of extinction memory was found in IE as compared to the DE. So many published studies support our observations (Chang and Maren, 2009, Chang and Maren, 2011, Thompson et al., 2010, Kim et al., 2010). However, some counteracts the data with IE (Myers et al., 2006). Our data is dependent on the decreased levels that were observed in any form of recovery in the early extinction. Moreover, this is quite hard to prove the statement of hypothesis. So, we finally conclude that the IE is less effective as compared to the DE, and this was supported by previous reports of Myers et al., 2006. While, Chang and Maren, 2009, reported that short term context independent suppression of fear after IE which was high mainly due to habituation not extinction. Apart from this in the present report we didn't use probe CS to test the extinction retention after extinction for 15 minutes and the deficit in retention of extinction as observed next day during the retention test was almost alike to published reports. Further studies are required for its confirmation. To make the data effective we correlate the changes usually occurring in the two subregions of brain mainly PL and IL of mPFC, which along with the amygdala and hippocampus. They are involved to regulate the consolidation and fear retention as well as memory extinction (Marek et al., 2013, Preston and Eichenbaum, 2013, Corcoran and Maren, 2001, Maren et al., 2013). DE and IE exhibited neuron activation in PL and IL subregion of mPFC as demarcated by the c-fos expression after extinction exposure. While, IL neuronal activity increment for DE was increased in relation to IE. Our results also support the previous reports (Thompson et al., 2010). However, some other reports showed

different for fear behavior regulated by PL in relation IL (Sotres-Bayon et al., 2006, Milad et al., 2004, Courtin et al., 2013) through up/down regulated neuron activation in these regions (Sierra-Mercado et al., 2011, Sotres-Bayon and Quirk, 2010) as suggested in our present report. The loss in retention of memory extinction as observed in the IE in our report and previously published other reports (Chang and Maren, 2009, Chang and Maren, 2011, Thompson et al., 2010, Kim et al., 2010). This is mainly due to the result of suppressed activation of IL neurons as well as electrical stimulation of mPFC which results in elimination of this loss (Kim et al., 2010). While expression of c-fos, we had looked at expression of CBP which was found to be increased in IL than that of IE which positively correlates with the expression of c-fos expression. As a known fact that CBP is associated with histone acetyltransferase and its increased activity results in the acetylation of histones H3/H4 which may modulate the expression of gene in the formation of memory (Peixoto and Abel, 2013). Our result suggested that there is decreased activity of neurons in IL of rats which fail to relate the fear as compared to extinguish fear normally. This usually associated with the lysine residues which are present in the core of histone proteins (Roth et al., 2001). This report predict that the neuronal activity in the IL and PL is associated with histone methylation. The methylation of H3/H4 at residues K9/K5 were increased in IL and PL regions following IE and DE and is usually associated with the massive change in CBP levels. Our major findings suggest long-term extinction is minimal when extinction is conducted for a short time after fear learning in rats and this loss is usually by the decreased neuronal activation in IL of rats which are in IE. This loss in longterm extinction is shown that it may be related to the level of histone methylation in the IL of the IE. The data from the present report may be useful in traumatic planning and execution of psychological and pharmacological interventions.

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Conflict of Interest

Authors declare no conflict of interest.

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