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ORIGINAL ARTICLE

Alteration in expression of histone deacetylase 11 mRNAs during cerebral cortex and hippocampal formation of embryonic and neonatal mouse brain

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Abstract

OBJECTIVES: Acetylation/Deacetylation status of core histone has been shown important in regulation of gene expression in developing brain. Few studies address the role of HDAC11 of class IV HDACs in postnatal brain development however; information regarding HDAC11 involvement in prenatal developing brain is totally absent. This, together with localized expression pattern of HDAC11 in restricted organs, prompted us to track its involvement in both pre- and postnatal developing parts of mouse brain.
METHODS: HDAC11 mRNAs levels were measured using qPCR method.
RESULTS: We demonstrate for the first time that the HDAC11 mRNA has an intensive elevated expression level during embryonic prenatal cortex formation at day 18 (E18) corresponding to the time when innervation with intensive neurite outgrowth occurs. HDAC11 mRNAs during postnatal cortex formation has an interesting expression pattern of fluctuation with two peaks at days 10 and 40 after birth (P10 and P40). The HDAC11 mRNAs quantities for developing postnatal hippocampus however, gradually increase with increasing age, peaking at P20.
CONCLUSION: We suggest that the pattern of prenatal HDAC11 expression positively correlate with neural cell formation and, with nucleosomal histone deacetylation. In addition, increasing HDAC11 expression in postnatal developing hippocampus as well as temporal and spatial expression pattern observed in postnatal developing cortex seem to be consistent with histone deacetylation and that this event may positively correlate with neural cell formation and/or maturation. We therefore conclude that HDAC11 gene plays a distinctive role in early developing murine brain.

Introduction

Epigenetic modification caused by acetylation of core histone proteins has been implicated in cellular development of the CNS. This remodeling of chromatin structure in response to different stimuli appears to be an ideal mechanism to generate continuous cellular diversity and regulate gene expression at successive stages of brain development (Liu *et al* 2009). Acetylation is a dynamic process supported by enzymatic activity of two counteracting enzyme families of histone acetyltransferases (HATs) and histone deacetylases (HDACs) which control the acetylation state of the ε–amino group of lysine side chains within

the N–terminal tails of core histones (Gallinari *et al* 2007). Histone acetylation by histone acetyl transferase neutralizes lysine positive charge and causes a reduction in interaction between histone and DNA, resulting in transcription activation. Histone deacetylase activity, on the other hand, results in hypoacetylation, chromatin condensation, and inhibition of transcription. Such reversible acetylation plays a central role in the regulations of transcriptional programming and brain plasticity (Levenson & Sweatt 2005; Barrett & Wood 2008; Borrelli *et al* 2008). To this end, although activation of specific genes is often correlated with histone acetylation (Jenuwein & Allice 2001, Roh *et al* 2005), the deacetylation and HDAC activity also play an important role in gene expression and cell development (Hao *et al* 2004, Haberland *et al* 2009). Furthermore, describing genome-wide mapping of HATs and HDACs binding to chromatin, Wang *et al* found that both HATs and HDACs are targeted to transcribed regions of active genes (Wang *et al* 2009). In addition and in some extends, distinct HDACs may play either positive or negative roles triggering the expression of distinct genes through their interactions with different groups of transcription factors (McKinsey & Olson 2004). Activity of HDAC is tightly controlled through targeted recruitment, protein–protein interactions and post–translational modifications. In fibroblast cells, HDAC11 mRNA abundance is correlated with proliferative status of these cells (Bagui *et al* 2013). As specific chromatin modifier, HDAC11 also epigenetically regulates brain-specific glycosyltransferase N-acetylglucosaminyltransferase-IX (GnT-IX) expression in brain by GnT-IX gene silencing (Kizuka *et al* 2014). Among the most important roles of these enzymes, the control of cell cycle progression, cell survival and differentiation can be addressed (Gallinari *et al* 2007).

It has been shown that in developing CNS, the acetylation of histones H3 and H4 gradually decreases with increasing the age of the animal (Piña *et al* 1988, Shen *et al* 2005). Similarly, acetylation level of H3 and H4 gradually decreases when the *in vitro* cultured adult rat hippocampal neural precursor cells were induced to differentiate by mitogen removal (Hsieh *et al* 2004). In addition, the suppression of HDACs expression by inhibitors of HDACs (HDACi) suppresses the normal development of some cells of neural origin both *in vitro* (Hsieh *et al* 2004) and *in vivo* (Shen *et al* 2005). It was shown that the use of some HDACi such as TrichostatinA (TSA) and Paclitaxel (*Taxol*) inhibits development of prenatal oligodendrocyte precursors (Liu *et al* 2003). Moreover, administration of "sub-apoptotic" levels of TSA and *n*-butyrate in mouse cultured neuroblastoma Neuro-2a and microglia N9 cells selectively inhibits the expression of some HDAC molecules, forcing them to over-express to compensate for the lost HDAC mRNAs. This suggests a role for HDAC molecules in differentiation of mouse malignant cells of neural origin (Ajamian *et al* 2004). Recent studies using HDAC inhibitors show HDAC genes not only are involved in progression of neurodegenerative disease (Cao *et al* 2018) but also they modulate normal neural plasticity and memory enhancement (Zhao *et al* 2018). Their role has also been shown in formation of mode disorders such as cognitive deficits and anxiety (Huang *et al* 2018) and Epilepsy (Reddy *et al* 2018). They have also been suggested as potential antiseizure drug target (Ibhazehiebo *et al* 2018). While histone acetylation is often related to gene activation, several studies have indicated that in the CNS, histone deacetylation can also promote neural cell development suggestting that HDACs activity plays a key role in gene expression in central nervous system (Liu *et al* 2008). Epigenetic control of gene expression also occurs via mechanisms such as histone methylation, histone phosphorylation, and DNA methylation (MacDonald & Roskams 2009). The molecules of HDACs belong to four different classes of enzymes (De Ruijter *et al* 2003), of which not all are necessarily expressed during CNS development. For example, although the roles of many members of classes I, II and III HDAC proteins – especially class II (Ajamian *et al* 2003) – in the regulation of neural cells development was to some extent elucidated in recent years, some HDACs are not expressed at all during this period. Available information about the role and function of class IV HDAC gene in this regards is quite limited. Recent studies have shown that most HDACs expressed in the adult brain of rat are predominantly in neurons (Broide *et al* 2007), although Liu *et al* more recently reported the postnatal developmental expression of histone deacetylase 11 in the murine brain; mostly in oligodentrocytes but minimally in neurons (Liu *et al* 2009). High levels of HDAC11 expression are restricted to a few organs, including brain, heart and kidney of both humans (Gao *et al* 2002) and mice (Liu *et al* 2009) suggesting an important role for HDAC11 in these organs. It was reported that HDAC11 protein contains conserved residues in the catalytic core regions shared by both class I and II mammalian HDAC enzymes and that the HDAC11 protein resides in the nucleus (Gao *et al* 2002). The regulatory role of HDACs including HDAC11 in mouse brain nucleus accumbens (mNAc) via HDAC2-dependent mechanisms has recently been reported (Torres *et al* 2016).

The exact mechanism(s) by which acetylation of histone is regulated in the brain remain to be elucidated. Although few studies have proposed a mechanism, linked to function of HDAC11 molecules in the first two weeks of "post"-natal developing rat and mouse brain (Liu *et al* 2009, Torres *et al* 2016), the available information in literature concerning HDAC11 mRNAs and/or protein expression changes in "pre-natal" developing CNS is totally absent. The aim of this study was to analyze the expression of histone deacetylase 11 mRNAs in the cerebral cortex and hippocampal of embryonic and neonatal mouse brain.

Methods and materials

Animals

NMRI mice were used in this study. The mice were maintained on 12:12 h light–dark cycle beginning at 8.00 a.m. They were kept at a constant temperature in mouse boxes with unrestricted access to food and water. The colony was maintained through random pair mating. Timed mating was carried out by placing a male and female together in a box and checking for the presence of a vaginal plug. The presence of a plug was taken to indicate successful mating and the time was taken as gestational day zero. All animal procedures including anesthesia and care of experimental animals used in this study were carried out in accordance with the Animals Scientific Procedure (Act, 1986) and, within the Guidelines of the Directive 2010/63/Eu of the European Parliament on the protection of animals used for scientific purposes.

Sampling

Cortex and hippocampus were dissected from postnatal days at 1, 5, 10, 20, 40 (P1, P5, P10, P20 and P40) and also cortical tissue from embryonic days 14 (E14), 18 (E18) and the onset day of pregnancy termination (E21). The gender of embryos and early postnatal pups were not clear and thus the potential gender biological effect(s) on the result of this study was not considered.

RNA extraction and cDNA synthesis

Total cellular RNA was extracted using Trizol@ Reagent (*Invitrogen, USA*) and 2μg of RNA was reverse transcribed to single-stranded cDNA using a RevertAid Tm kit (*Fermentase, Lithuania (Thermo Fisher Scientific)*) and *oligo dT* according to the manufacturer's protocol.

Quantitative real–time polymerase chain reaction (qRT–PCR):

Messenger RNA expression level of HDAC11 was evaluated using an SFX machine (*BioRad*, *USA*). Amplifications were obtained using Real-time-PCR Master Mix E3 (*GeneON, Germany*) and mouse HDAC11 specific primers. The sequences for the mouse HDAC11 forward and reverse primers were 5'-AATGGGGCAAGGTGATCAAC-3' and 5'-CATCAATGTTGGTGGTGGCT-3', respectively and were designed using primer3 software (*University of Massachusetts Medical School*). To quantify mRNA abundance, a standard curve for mouse HDAC11 mRNA was generated from serial dilutions of cDNA obtained from either an adult mouse whole brain, E21 or P1. The relative abundance of *HDAC11* mRNA was estimated based on standard curve and all data were normalized against mouse GAPDH and 18S rRNA abundance.

Statistical analysis

Comparison of gene expression was performed between groups by one–way ANOVA and Duncan test. The levels of significance were set at $p \leq 0.05$.

Results

Using real time polymerase chain reaction (qPCR) we have quantified the HDAC11 of class IV Histone deacetylase mRNA abundances in dissected regions of both developing *pre*-and postnatal developing cortex. We have also measured mHDCA11 mRNA levels in postnatal developing hippocampus during murine brain development.

We have shown for the first time that mRNA levels for the class IV HDACs increase at a certain time points during *pre*-natal development of mouse cortex i.e. E14 and E18. As indicated in Figure 1, the highest level for HDAC11 mRNA abundance was observed in day E18 which was two times more than that in day E14 (Figure 1). We have also shown that in accordance with results published by other researchers (Liu *et al* 2009), the expression in HDAC11 mRNA levels changes in a temporal and spatial pattern in postnatal developing cortex; as well as in postnatal developing mice hippocampus. This temporal and spatial pattern of HDAC11 mRNA expression seems to correlate positively with neural cell formation/maturation.

As quantified by real time quantitative PCR, the abundance of mouse HDAC11 mRNA increases during day E14 to- day E18 of *pre*-natal brain with the highest level of HDAC11 transcripts seen in E18 (Figure 1). This means that the level of mHDAC11 RNA at E18; i.e. the time of stratification of cortex formation, was at high as twice in compare to its initial level at day E14. The peak in the expression of HDAC11 gene may indicate its involvement in the intensive neurite outgrowth stage of prenatal brain formation. After reaching a peak in day E18, the intensity of HDAC11 transcripts significantly drops in the last day of pregnancy at its termina-

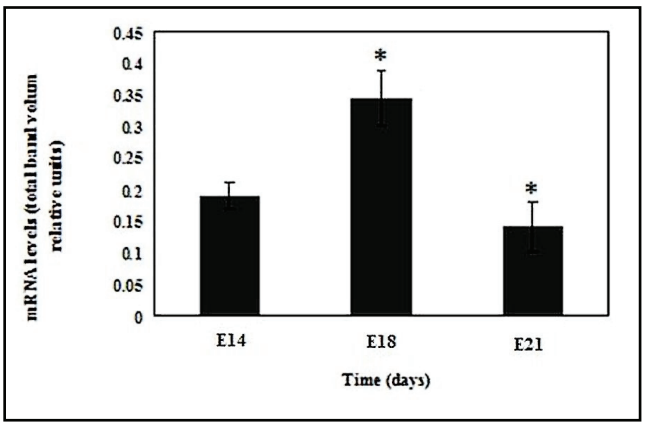

Fig. 1. Alteration in expression of mHDAC11 mRNAs in cerebral cortex (CTX) during *pre*-natal mouse brain development. The quantity of HDAC11 transcripts reaches a peak at day 18 of embryonic development. The mRNAs abundances were measured relative to that of E21 whole brains and were normalized to both of 18s rRNAs (18s) and GAPDH housekeeping genes transcription levels. Values represent mean ±SEM from at least 6-8 samples. Asterisks indicate statistical significance (*$p \leq 0.05$).

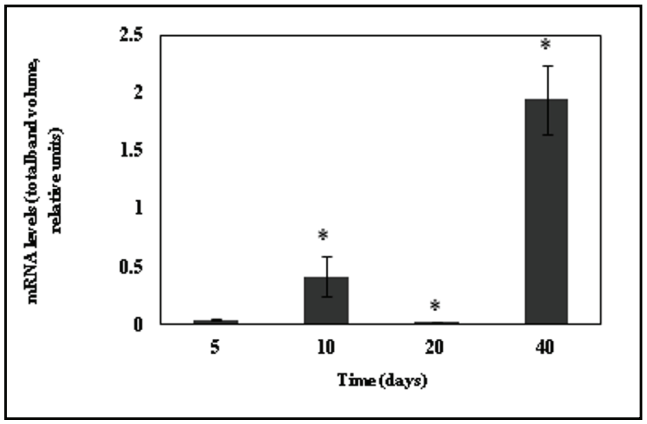

Fig. 2. Alteration in expression of mHDAC11 transcripts in cerebral cortex (CTX) during postnatal mouse brain development. Obvious reduction of HDAC11 mRNA is seen at day 20 after birth. The mRNAs abundances were measured relative to that of P1 whole brains and were normalized to both of 18s rRNAs (18s) and GAPDH housekeeping genes transcription levels. Values represent mean ±SEM from at least 6-8 samples. Asterisks indicate statistical significance (*$p \leq 0.05$).

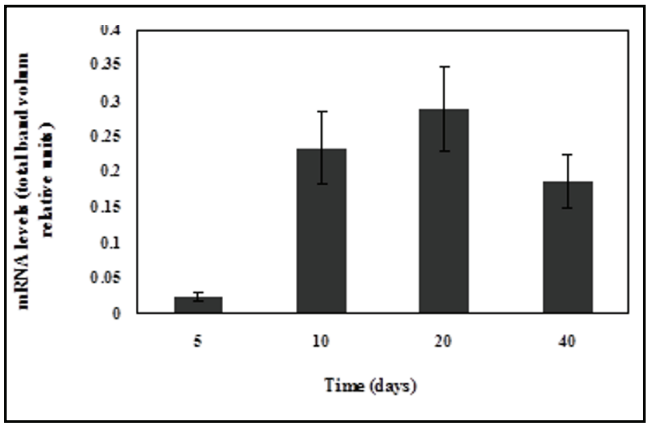

Fig. 3. Relative expression of HDAC11 mRNA in hippocampal regions of mouse brain during postnatal development: The expression level reaches up to 30 folds higher for P20, if compare with those measured at birth. Data obtained by qRT-PCR analysis and were normalized against 18S rRNA and GPDH probes as internal controls. Values represent mean ±SEM from at least 6-8 samples. (*$p \leq 0.05$).

tion [E21] (Figure 1), so that at the onset of birth, the abundance of HDAC11 mRNA dramatically reduces to a level lower than its initial level at day E14.

We couldn't measure HDAC11 mRNA abundance before day E14 due to technical difficulty associated with dissociation and isolation of interested region(s); and/or technical difficulty in extraction of RNAs. Although the postnatal hippocampal HDAC11 mRNA expression pattern was studied, the HDAC11 mRNA abundance was not measured in prenatal hippocampus due to the same difficulties in tissue isolation/dissociation and/or due to RNA extraction failure.

When comparing relative HDAC11 mRNA abundance in postnatal cortex tissues, two peaks at second week (at day 10) and at sixth week (at day 40) have been observed (Figure 2). The expression levels compared to levels observed at birth, reach 4 and 10 folds higher for day P10 and day P40, respectively. In contrast, for the two remaining points quantified after birth i.e. day 5 (P5, first week) and day 20 (P20, third week), the HDAC11 mRNA expression remain almost constant and no significant changes were seen (Figure 2). We did not study the events, which will potentially occur in days after P40. We also didn't measure the expression of HDAC11 protein and its potential fluctuation in the time points studied.

For the postnatal hippocampal tissues, the schema of HDAC11 gene expression is almost in line with its *pre*-natal expression pattern. The expression level rapidly increases from day 5 (P5) to the day 10 (P10) and gradually to day 20 (P20) and then decreases to day 40 (P40) (Fig. 3). The expression level reaches up to 30 folds higher for P20, in comparison with those measured at birth. However, the expressed quantity of HDAC11 mRNA does not drop to its initial level at day 5th, immediately after birth (P1) (Figure 3).

All data are relative expression quantities of HDAC11 mRNA expression when compared to that of whole brain samples at E21 for *pre*-natal and P1 for postnatal which were used to design and perform the standard curves for real time quantification of polymerase chain reactions. All results are normalized against that of mouse housekeeping mRNA transcripts of GAPDH and 18S ribosomal RNA genes. The RNAs quality and expressed mouse HDAC11 gene during *pre*-natal cortex development are shown in Figure 4, as example.

Discussion

In the present study we have demonstrated that the level of HDAC11 transcripts – which is the only found member of class IV histone deacetylases genes – changes during both *pre*- and postnatal CNS development in the brain of laboratory mice.

We have shown for the first time that in the developing "*pre*-natal" mice brain, the HDAC11 gene is not only expressed but also its mRNA transcripts have an elevated expression pattern in day E18 of *pre*-natal cortex formation. We have also shown that HDAC11 expression exhibits a spatial, temporal and special pattern which seems to be consistent with histone acetylation and that it might positively correlate with neural cell formation and/or maturation.

As mentioned earlier, the amount of HDAC11 mRNAs for developing postnatal hippocampus gradually increases from day 5 to 20 after birth and then, decreases to day 40 (Figure 3). In the developing postnatal cortex however, the cortical HDAC11 mRNAs abundance has a temporal and spatial pattern of expression with two peaks of expression at days 10 and 40 (Figure 2). On the other side, the abundance of HDAC11 transcripts at days 5 and 20 are almost constant in line to the amount measured at birth. This hap-

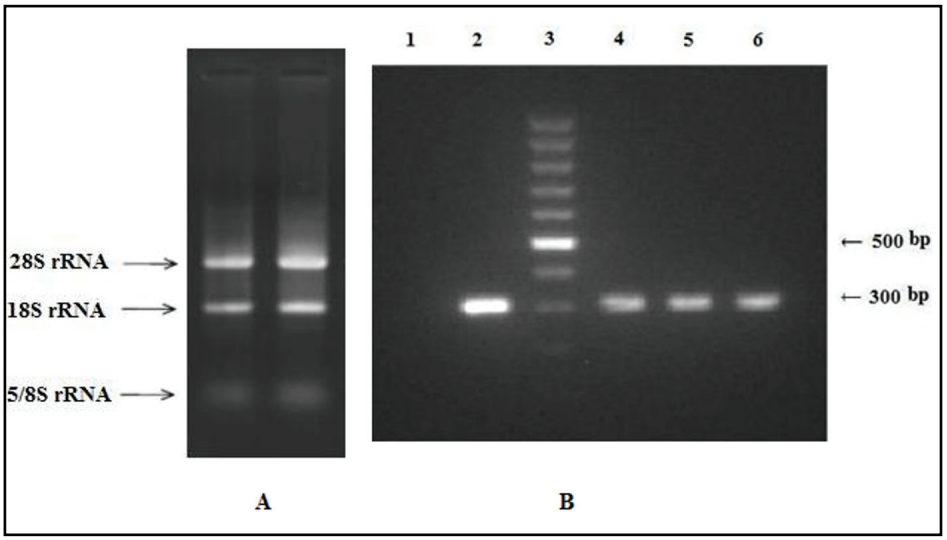

Fig. 4. Example of RNA quality in mHDAC11 expression: The integrity confidence of extracted total RNAs from mouse developing cortex and expressed HDAC11 gene are shown in this figure: **A)** Total RNAs extract from day E 18 of prenatal developing cortex and **B)** the expressed mHDAC11 transcripts from developing prenatal cortex at day E14 (line 4), day E18 (line 5) and day E21 (line 6). Line 1; negative control (no cDNA), line 2; positive control (cDNA of a whole brain sample) and line 3; 100bp DNA marker.

pens while a slight reduction can still be seen at day 20 which is even lower than the level measured at days 5 (and further compare to day 1 (Figure 2; data for P1 is not shown). This observation is roughly in accordance with the finding reported by other authors: Liu et al, demonstrated that the mouse cortical HDAC11 transcripts have elevated levels at days 10 and 40 in developing postnatal brain when compared with those measured at 5 and 20 (Liu *et al* 2009). Obvious reduction of HDAC11 mRNAs at day 20 is seen in both our and in their work. Liu *et al* have also shown that, consistent with the changes in mRNA expression, the abundance of assessed HDAC11 protein in parts of developing brain – such as cortex – increases significantly during development and then gradually with their maturation, either growing and/or maturating oligodendrocytes and neurons react to HDAC11-specific antibody in many parts of developing brain including cerebral cortex and hippocampus (Liu *et al* 2009). We would suggest that this temporal and spatial pattern of HDAC11 gene expression may positively correlate with neural cell maturation and with nucleosomal histone deacetylation since the results of hippocampal expression pattern of HDAC11 gene in our experiments are the same as those observed by Liu *et al* in the above mentioned work.

Although it is generally accepted that histone deacetylation activity of HDACs is associated with gene silencing in many cell types/tissues, several studies have demonstrated that in the Central Nervous System (CNS), in contrast, histone deacetylation is linked to neural gene expression/activation (reviewed by Siebzehnrubl *et al* 2007) and neural cell development (Rosenqvist *et al* 2002, Hsieh *et al* 2004, Shen *et al* 2005, Balasubramaniyan *et al* 2006). Acetylatation of histones H3 and H4 has been reported to gradually decrease in the oligodendrocyte-rich regions of corpus callosum during rat postnatal development (Shen *et al* 2005) and with cell maturation in cortical neurons of rat (Piña *et al* 1988). The significantly increased levels of HDAC11 mRNA in developing postnatal mouse cortex and hippocampus shown in this study, in accordance with results observed by others, is simultaneous with significantly decreased acetylation of histones H3 and H4, which may indicate the contribution of HDAC11 gene in these histone genes deacetylations. The confirmed ability of HDAC11 gene to remove an acetyl group from core histone proteins such as H3 and H4 has been proven (Gao *et al* 2002). In addition, the increased amount of histone H3 acetylation in cultured oligodendroglial cell line can be achieved by suppressing HDAC11 gene expression using RNA interference technology (Liu *et al* 2009).

We have previously shown the up-regulation of only class II of HDACs i.e. HDAC5, HDAC6, HDAC7 and HDAC9 expression in the cultured rat hippocampal neural precursors during their maturation (Ajamian *et al* 2003). Although HDAC11 is considered to be more closed to Class I of HDACs (as it will be discussed below), the finding of current study may still suggest a role for HDAC11 molecule in reduction of histone acetylation levels during *pre-* and postnatal mouse brain development similar to that was seen in our previous results mentioned above (Ajamian *et al* 2003).

We observed that the quantities of HDAC11 transcripts increase during days E14 to E18 of *pre*-natal brain formation which then decreases before the day of termination of pregnancy at day E21. In *pre*-natal developing cortex, the day E18 is the time when innervation with intensive neurite outgrowth occurs i.e. the time that in our results correlates with intensive expression of HDAC11 mRNA in *pre*-natal cortex. Methyl green staining of cortex during prenatal development also shows differences in morphology and stratification of cortex tissue, which can easily be seen between days E14 to E18 with a gradually increasing differentiation pattern (Figure 5). As shown in Figure 1, the amounts of HDAC11 mRNA then significantly decrease from

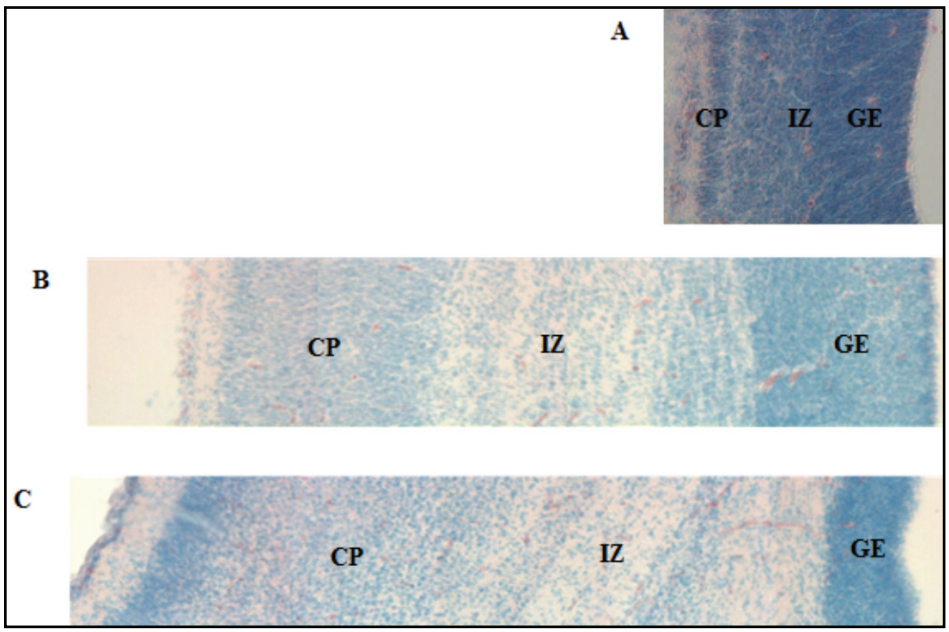

Fig. 5. Methyl green staining of prenatal developing cortex: Morphology changes with a gradually increasing differentiation pattern of prenatal cortex tissue in mice brain from days E14 (**a**) and E18 (**b**) to onset of birth; E21 (**c**). Scale bar = 5μm. **CP**; Cortical plate; **IZ**; Intermediate zone; **GE**; Germinal epithelium.

day E18 and dramatically drop to a level lower than its initial level in day E14, just at the onset day of pregnancy termination [E21] (Figure 1).

We suggest that the pattern of *pre*-natal HDAC11 gene expression may positively correlate with neural cell formation and/or maturation, and with nucleosomal histone deacetylation. Development of the cerebral cortex is a dynamic process that involves coordinated neurogenesis and neuronal migration. Both neuronal differentiation and migration have been found in their high levels during days E14.5–15.5 (Montgomery *et al* 2009). Through tissue studies, it is apparent that stratification of cortex occurs during E14–E18 and as observed, this is the time when HDAC11 gene expression increases. A relatively new study has shown that HDAC1 and HDAC2 of class I HDACs are specific and critical components of the neuronal differentiation program (Montgomery *et al* 2009). On the other hand phylogenetic analyses show that HDAC11 is most closely related to HDAC3 and HDAC8, suggesting that it might be more closely related to the class I HDACs than to class II (Broide *et al* 2007). We therefore conclude that this conserved, but newly found HDAC11 molecule may play a role in neuronal differentiation in *pre*-natal development of cortex, as do HDAC1 and HDAC2. We speculate that the over-transcribed copies of HDAC11 molecule may in fact, reflects the involvement of this gene in important processes of brain formation such as neurogenesis. The increased expression of HDAC11 in prenatal cortex in this study may also demonstrate a role for this gene during *pre*-natal neural cell formation and differentiation.

In conclusion our data suggest that HDAC11 gene play an important role in regulation and modification of core histones in the distinctive part of mice developing brain i.e. hippocampus and cortex during *pre*- and post-natal development. Our data suggest that mouse HDAC11 gene acts as an important regulator of gene expression during murine brain formation and development although the exact function(s) of elevated HDAC11 remain to be determined.

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