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Research report

Differential regulation of multiple brain-derived neurotrophic factor transcripts in the postnatal and adult rat hippocampus during development, and in response to kainate administration

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Abstract

Brain-derived neurotrophic factor (BDNF) is expressed at high levels in the hippocampus, where it has been implicated in physiological functions such as the modulation of synaptic strength as well as in the pathophysiology of epileptic seizures. BDNF expression is highly regulated and the BDNF gene can generate multiple transcript isoforms by alternate splicing of four 5′ exons (exons I–IV) to one 3′ exon (exon V). To gain insight into the regulation of different BDNF transcripts in specific hippocampal subfields during postnatal development, exon-specific riboprobes were used. Our data shows that BDNF exon I and exon II mRNAs are regulated in hippocampal subfields during postnatal development, in contrast to BDNF exon III and exon IV mRNA, which remain relatively stable through this period. Further, exons I and II show distinct temporal patterns of expression in the hippocampus: BDNF I mRNA peaks in adulthood in contrast to BDNF II mRNA which peaks at postnatal day 14 (P14). Finally, we have addressed whether kainate treatment in postnatal pups and adults regulates BDNF through the recruitment of the same, or distinct, BDNF promoters. Our data indicates that kainate-induced seizures induce strikingly different expression of distinct BDNF transcripts, both in magnitude as well as spatial patterns in the hippocampal subfields, of pups as compared to adults. These results suggest that kainate-mediated seizures differentially recruit BDNF promoters in the developing postnatal hippocampus in contrast to the adult hippocampus to achieve a hippocampal subfield specific regulation of exon-specific BDNF mRNAs.

Theme: Development and regeneration
Topic: Neurotrophic factors: expression and regulation

Keywords: Brain-derived neurotrophic factor promoter; Seizure; Hippocampal development; Neurotrophin

1. Introduction

Brain-derived neurotrophic factor (BDNF) is the most abundant and widely distributed neurotrophin in the brain [25,45], with the highest expression in the hippocampus. BDNF plays a critical role in the survival, differentiation and maintenance of neuronal populations during development [38]. In the mature brain, BDNF exerts a profound influence on both structural and synaptic plasticity [23,38]. In particular, brain regions like the hippocampus which exhibit considerable postnatal development, and retain the ability for neurogenesis and axonal sprouting in adulthood, are important targets of BDNF. Within the hippocampus, BDNF has been implicated in both normal physiological functions as well as the pathophysiological changes that arise from neuronal insults. A physiological role for BDNF in activity-mediated synaptic plasticity in the hippocampus is supported by several studies which indicate that BDNF enhances excitatory neurotransmission [15] and quantal neurotransmitter release [43], and may influence both short-

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term and long-term synaptic strength and morphology [16,23,26,32]. BDNF has also been implicated in the pathogenesis of epileptic seizures and indeed several studies suggest that BDNF contributes to seizure-induced damage, axonal sprouting, seizure threshold and epileptiform activity in the hippocampus [4,19].

Hippocampal BDNF expression is developmentally regulated, activity-dependent and dramatically induced in response to seizures [14,25,27]. The BDNF gene has a complex structure and the expression of BDNF transcripts is highly regulated. Eight unique BDNF transcripts can be generated through the alternate splicing of four distinct 5′ exons (exons I–IV) to a common 3′ exon (exon V) and by the use of two polyadenylation sites [40]. The 5′ exons, each with their own promoters, remain untranslated and only the common 3′ exon generates mature BDNF protein. All BDNF transcript forms are present within the hippocampus [5,28] and differential recruitment of the multiple BDNF promoters results in distinct BDNF transcript forms being regulated by physiological stimuli such as diurnal rhythm [3] and pathophysiological insults such as seizures and ischemia [18]. Previous studies examining the regulation of BDNF mRNA following kainate-mediated seizures in both postnatal and adult animals did not examine the regulation of the different BDNF transcript isoforms [8,20]. Thus, at present, it is unknown if seizure generation in postnatal animals as compared to adults regulates BDNF expression through the recruitment of the same, or distinct, BDNF promoters. We have addressed the kainate-mediated regulation of exon-specific BDNF transcripts in pups as compared to adults. In addition, we have also evaluated the expression of multiple BDNF mRNAs in specific hippocampal subfields across postnatal development. Although a previous study has demonstrated the developmental regulation of multiple BDNF transcripts through postnatal development [41], they utilized RNase protection assays that did not provide any information on the regional expression of the multiple BDNF transcript forms in hippocampal subfields. Given the important role of BDNF in structural and synaptic plasticity within the hippocampus, analysis of the role of multiple BDNF promoters in the hippocampus during postnatal development and in response to seizures in the postnatal and adult hippocampus will provide insights into the molecular mechanisms that control the expression of multiple BDNF transcripts.

2. Materials and methods

2.1. Animal treatment paradigms

Sprague–Dawley rats bred in our animal-breeding colony were used in all experiments. All animal procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the TIFR Institutional Animal Ethics Committee. For the developmental expression study, animals on postnatal day 0 (P0), P4 and P14 were used (n=5/group) with P0 denoting the date of birth. Male Sprague–Dawley rats (>70 days) were used for the adult group (n=4). For the kainate treatment study, Sprague–Dawley rats on P5 and adult animals were used (n=4–5/group). Animals from the P5 group received 5 mg/kg of kainate intraperitoneally (i.p.) or saline treatment. This dose of kainate was chosen based on previous studies, which indicate reliable behavioral and electrographic seizure generation [20,42]. Animals were sacrificed 6 h post saline or kainate administration. Adult rats received saline or 10 mg/kg of kainate i.p. and were sacrificed 6 h post-treatment.

2.2. Tissue preparation and in situ hybridization

All animals were sacrificed by rapid decapitation and the brains were frozen on dry ice followed by storage at −70 °C. 14 μm thick coronal sections were cut on the cryostat and slides were fixed in 4% paraformaldehyde, acetylated and dehydrated. In situ hybridization was carried out using a previously described protocol [6]. In brief, rat exon-specific BDNF cRNA probes were transcribed using ^{35}S-labeled UTP (Amersham, Buckinghamshire, UK) and were generated from plasmids provided by Dr. Lauterborn (University of California, Irvine). Slides were incubated with the BDNF exon-specific riboprobes (1×10^6 cpm/slide) for 20 h at 60 °C. The sections were then subjected to RNase A (20 μg/ml) at 45 °C for 30 min followed by stringent washes in decreasing concentrations of SSC. Slides were air dried and exposed to Hyperfilm β-max (Amersham, UK) for 6 weeks. Sense riboprobes for the different BDNF exons, a ribonuclease (40 μg/ml at 37 °C for 30 min) pre-hybridization wash, or competition with excess cold antisense riboprobe for the different BDNF exons did not yield significant hybridization (data not shown) confirming the specificity of the signal observed with the exon-specific antisense riboprobes.

2.3. Quantitation and data analysis

Levels of BDNF transcripts containing specific exons (I–IV) were quantitated using Scion Image software (Scion, USA). ^{14}C standards were used to calibrate the autoradiography film and to correct for non-linearity. The dentate gyrus (DG), CA3 and CA1 were analyzed. An equivalent area was outlined for each sample and optical density measurements from both sides of three to four individual sections from each animal were analyzed, from which the mean value was calculated. Results were subjected to statistical analysis using the Student's t-test for experiments with two groups, or analysis of variance (ANOVA) followed by a Tukey–Kramer post-hoc test for experiments with more than two groups. Differences were considered to be statistically significant at p-values <0.05.

3. Results

The distribution and expression of different BDNF transcripts in specific hippocampal subfields was examined using radioactive in situ hybridization with sequence-specific riboprobes for each BDNF exon (exons I–IV). Densitometric analysis to quantify levels of specific exon-containing BDNF mRNAs was carried out in the DG, CA3 and CA1 hippocampal subfields.

3.1. Differential regulation of specific exon-containing BDNF mRNAs in hippocampal subfields during postnatal development

The expression of specific exon-containing (exons I–IV) BDNF transcripts in the DG, CA3 and CA1 subfields was examined at postnatal days 0, 4, 14 and in adult (>70 days) animals. The hippocampal expression of exons I and II BDNF transcripts across postnatal development is shown in representative autoradiograms in Fig. 1. The quantitation of the changes observed in exons I-, II-, III- and IV-containing BDNF transcripts during postnatal development in the hippocampal subfields is presented in Fig. 2. The results indicate that exon I- and exon II-containing BDNF transcripts undergo developmental regulation in the CA1, CA3 and DG regions of the postnatal hippocampus. In striking contrast, exons III- and IV-containing BDNF mRNAs are maintained at stable levels in these hippocampal subfields at the postnatal ages examined.

Although both exon I and exon II BDNF transcripts exhibit developmental regulation in the postnatal hippocampus, the results reveal that the pattern of regulation observed for BDNF I and BDNF II transcripts is markedly different. BDNF exon I transcripts peak in adulthood in both the CA1 and DG hippocampal subfields, whereas in the CA3 region BDNF I mRNAs already achieve maximal levels at P14 and are maintained at the same level in adulthood (Figs. 1 and 2). The results indicate that BDNF exon I mRNAs are significantly increased in the adult hippocampus as compared to the postnatal hippocampus. In contrast, BDNF exon II mRNAs peak at postnatal day 14 in both the CA3 and DG hippocampal subfields while in the CA1 BDNF exon II transcripts maintain stable levels at all postnatal ages examined with a significant decrease being observed in the adult CA1 hippocampal subfield (Figs. 1 and 2). The results indicate that BDNF exon II mRNAs are at their highest in the postnatal hippocampus as compared to the adult hippocampus.

3.2. Regulation of exon I- and exon II-containing BDNF transcripts in the postnatal and adult hippocampus following kainate-induced seizures

The effect of kainate-induced seizures on the expression of distinct exon-containing BDNF mRNA transcripts in specific hippocampal subfields was examined in pups (postnatal day 5) and adult animals (>70 days). As previously described [8,20,42] pups administered systemic kainate developed seizures in 20–30 min, exhibiting chewing behavior and forelimb tonico–clonic activity. Adult animals treated with kainate exhibited generalized limbic seizure activity.

Kainate-induced seizures significantly induced BDNF exon I mRNA levels in the CA3 and DG but not CA1 of postnatal pups and in the CA1, CA3 and DG of adult animals (Fig. 3A,B). The pattern of induction of BDNF I mRNA in the hippocampal subfields was different in pups in contrast to adult animals. Pups exhibited the highest elevation of BDNF exon I transcripts in the CA3, whereas the highest induction in the adults was seen in the DG.

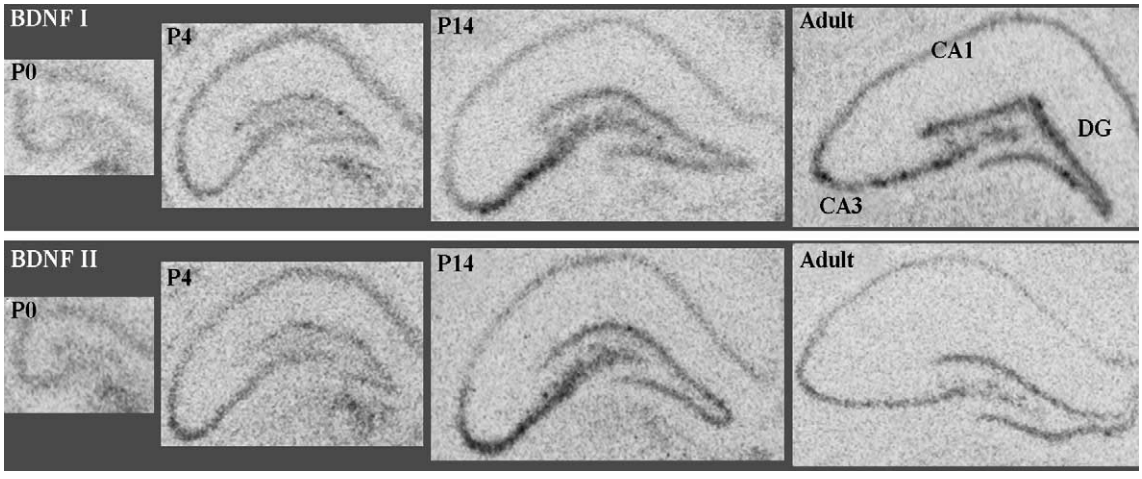

Fig. 1. Regulation of BDNF exon I and exon II transcripts in the hippocampus during postnatal development. Rats were sacrificed at P0, P4, P14 and adult (>70 days), and levels of BDNF transcripts were determined by in situ hybridization using exon-specific riboprobes. Representative autoradiograms from the hippocampal region of animals sacrificed at different postnatal ages are shown for exon I and exon II containing BDNF transcripts. The CA1, CA3 and DG are indicated.

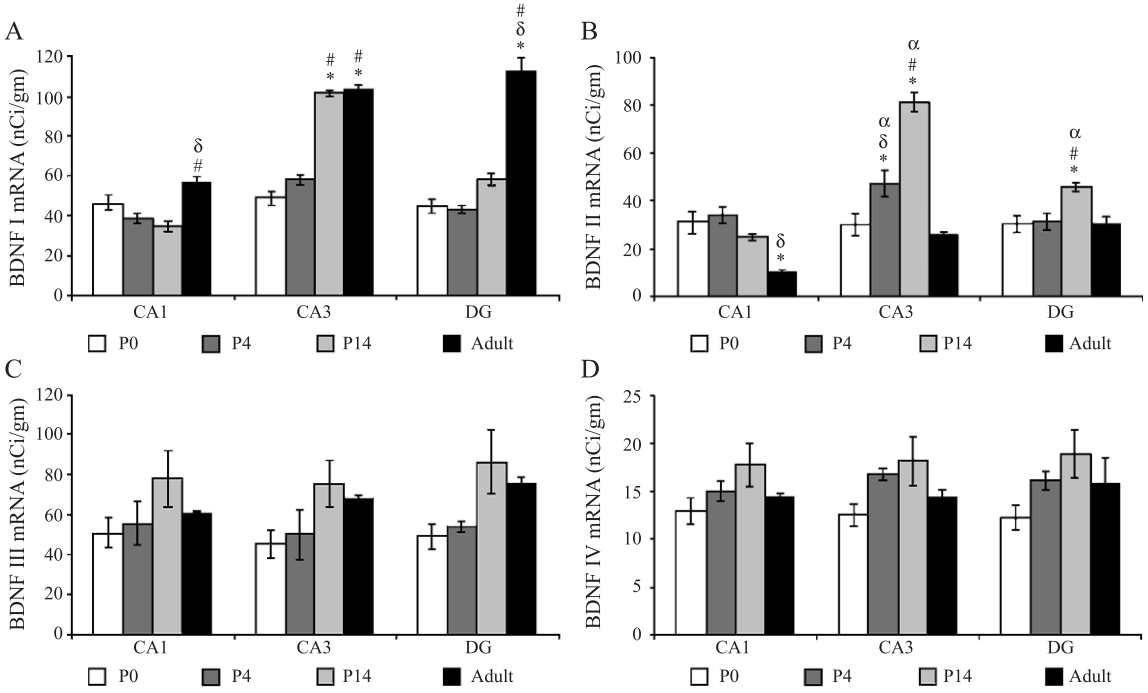

Fig. 2. Age-dependent expression of exon-specific BDNF transcripts (exons I–IV). Animals were sacrificed at four different postnatal ages—P0, P4, P14 and adult. Levels of BDNF transcripts containing specific exons (I–IV) were determined by in situ hybridization using riboprobes specific to the distinct BDNF exons (I–IV). Quantitation of the levels of different BDNF transcripts (exons I–IV) was performed using densitometric analysis. Levels of BDNF exon-specific mRNA levels in the CA1, CA3 and DG are shown. (A) Exon I, (B) exon II, (C) exon III and (D) exon IV. The results are represented as nCi/g and are the mean±S.E.M. (n=4–5/group). *p<0.05 in comparison to P0; $^{\#}p$<0.05 in comparison to P4; $^{\delta}p$<0.05 in comparison to P14; $^{\alpha}p$<0.05 in comparison to adult (one-way ANOVA, post-hoc Tukey–Kramer test). The scales for the y-axis differ between graphs for distinct BDNF exon-containing mRNAs.

BDNF exon I mRNA showed a 40-fold increase in the DG of adult animals sacrificed 6 h after systemic kainate administration, in contrast to the six-fold upregulation of exon I-containing BDNF transcripts seen in kainate-treated pups (Fig. 3A,B). The induction in BDNF exon I mRNA observed in pups was most often restricted to the crest of the dentate gyrus (Fig. 3A), in contrast to the induction in BDNF exon I observed in adults which was evenly distributed along the crest-tip axis in both blades of the dentate gyrus (Fig. 3B). The fold induction observed in BDNF exon I transcripts in the CA3 following kainate was similar in both pups and adults (~12–15-fold).

Exon II-containing BDNF transcripts exhibited a six-fold induction in the DG of adult animals treated with kainate with no significant changes observed in the CA1 or CA3 regions (Fig. 3D). In contrast, no significant changes were observed in BDNF exon II mRNAs in the CA1, CA3 or DG in kainate-administered pups in comparison to controls (Fig. 3C). Although exon II mRNA levels showed a trend towards an increase in the CA3 region of kainate-treated pups (Fig. 3C), this did not achieve significance (p=0.06).

Kainate-mediated regulation of exons I and II BDNF transcripts differed in both the magnitude and pattern at both ages examined, adult and postnatal. In adulthood, kainate-mediated increases in BDNF I mRNAs were greater in magnitude and observed in all hippocampal subfields examined in comparison to the kainate upregulation of BDNF II transcripts, which was restricted to the DG. In the pups, robust increases were observed in exon I BDNF transcripts in the CA3 and DG, while no significant change was seen in exon II-containing BDNF mRNAs.

3.3. Regulation of exon III- and exon IV-containing BDNF transcripts in the postnatal and adult hippocampus following kainate-induced seizures

Kainate-induced seizures regulated exon III- and exon IV-containing BDNF transcripts in a similar fashion. In adult animals, kainate resulted in increased levels of both exon III and exon IV BDNF mRNAs in the DG with no significant change seen in either of these transcript forms in the other hippocampal subfields at 6 h after kainate treatment (Fig. 4B,D). The magnitude of induction was greater for exon III BDNF transcripts (3.5-fold) in contrast to BDNF IV mRNAs (2-fold). In contrast, the upregulation of BDNF III and IV transcript isoforms was restricted to the CA3 region in pups administered kainate (Fig. 4A,C) with no changes in the DG. The magnitude of induction observed in BDNF III (1.8-fold) and IV (2-fold) mRNAs in the CA3 in kainate-treated pups was similar. For both exons III and IV BDNF transcripts, the regulation observed in pups and

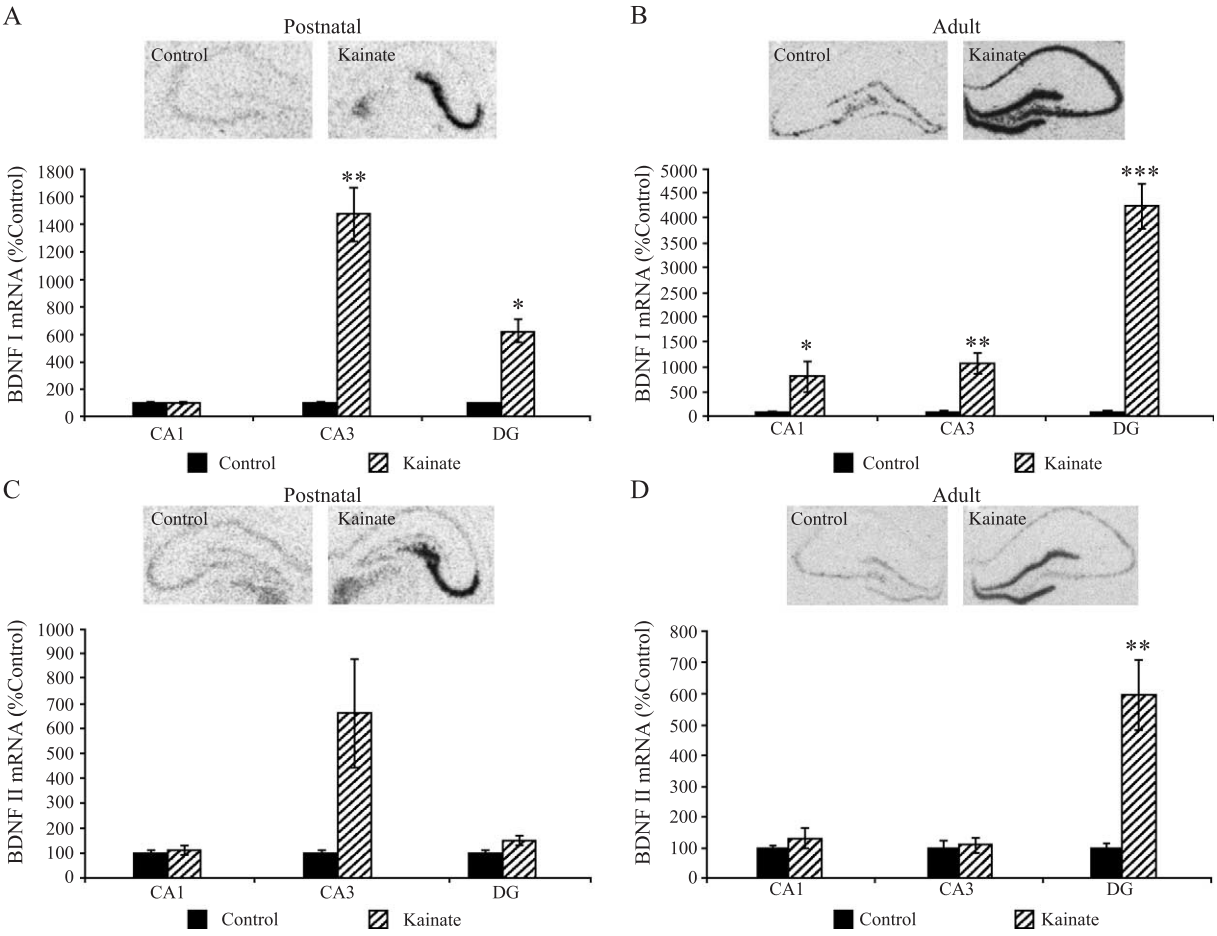

Fig. 3. Regulation of BDNF exon I and exon II transcripts within the hippocampus of P5 and adult animals in response to kainate administration. P5 pups and adult animals were administered either vehicle or kainate treatment and were sacrificed 6 h later. Levels of BDNF exon I and exon II transcripts were determined using in situ hybridization with exon-specific riboprobes and were quantitated using densitometric analysis. The levels of BDNF exon I and exon II mRNAs in the CA1, CA3 and DG of postnatal (A=exon I and C=exon II) and adult animals (B=exon I and D=exon II) are shown along with representative autoradiograms. The results are represented as percent of control and are the mean±S.E.M. (n=4–5/group). *p<0.05, **p<0.001, ***p<0.0001 in comparison to control (Student's t-test). The scales for the y-axis differ between the four graphs.

adults differed dramatically in the pattern, with induction restricted to the CA3 in pups and to the DG in adults.

4. Discussion

The results of our study demonstrate a differential regulation of exon-containing BDNF mRNAs in hippocampal subfields during postnatal development. Each 5′ exon has a separate promoter upstream suggesting that differential recruitment of the four distinct BDNF promoters may contribute to the hippocampal subfield-specific changes observed in exon-specific BDNF mRNAs across postnatal development. The data from our study revealed that BDNF exon I and exon II transcripts, in striking contrast to exons III and IV transcripts, are dramatically regulated across postnatal development in the dentate gyrus, CA3 and CA1 regions. Interestingly, while both exon I and exon II BDNF mRNAs exhibit regulation in the postnatal hippocampus, their pattern of regulation is remarkably different. While BDNF exon I mRNA levels are significantly higher in the adult hippocampal subfields, BDNF II mRNA expression appears to peak during postnatal development (P14) and is at lower levels in adulthood.

Previous studies [10,11,14,25] examining the regulation of BDNF expression across postnatal development were carried out using probes directed at the BDNF coding exon V and did not distinguish among BDNF transcript isoforms. The results of these studies demonstrated that hippocampal BDNF expression is lower during embryonic development and increases with maturation, reaching a peak at postnatal day 15 [10,11,14,17,25]. The present study indicates that the postnatal regulation of BDNF mRNA in the hippocampus is likely to primarily result from recruitment of exon I and II BDNF promoters. Our results also suggest that the peak in BDNF mRNA observed in the CA3 during the second postnatal week is likely to involve both exon I and exon II BDNF transcripts, while the peak observed in the DG may result predominantly from recruitment of the exon II BDNF promoter. A previous study [41] using RNase protection

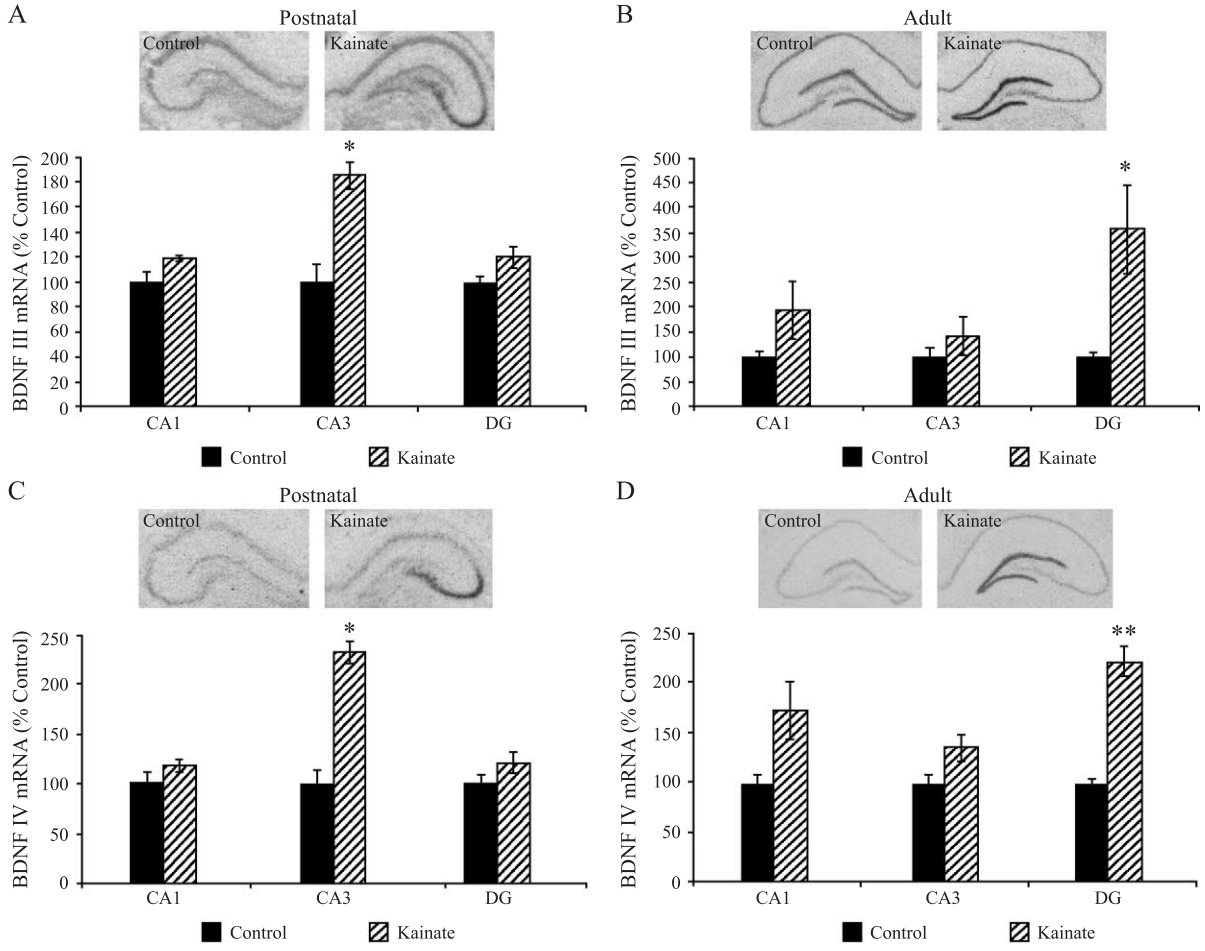

Fig. 4. Regulation of BDNF exon III and exon IV transcripts within the hippocampus of P5 and adult animals in response to kainate administration. P5 pups and adult animals were administered either vehicle or kainate treatment and were sacrificed 6 h later. Levels of BDNF exon III and exon IV transcripts were determined using in situ hybridization with exon-specific riboprobes and were quantitated using densitometric analysis. The levels of BDNF exon III and exon IV mRNAs in the CA1, CA3 and DG of postnatal (A=exon III and C=exon IV) and adult animals (B=exon III and D=exon IV) are shown along with representative autoradiograms. The results are represented as percent of control and are the mean±S.E.M. (n=4–5/group). *p<0.05, **p<0.001, ***p<0.0001 in comparison to control (Student's t-test). The scales for the y-axis differ between the four graphs.

assays has assessed the regulation of exon-specific BDNF mRNAs across postnatal development. This study indicated that all BDNF transcript isoforms in the hippocampus undergo a similar regulation, with lowest levels at postnatal day 1 followed by an increase at the end of the first postnatal week and steady levels being maintained into adulthood. Our results reveal a more complex postnatal regulation of exon-specific BDNF mRNAs in specific hippocampal subfields. The discrepancies observed between our results and the previous report [41] are likely to arise from the differences in techniques, and the fact that in our study we have examined expression in hippocampal subfields in contrast to total hippocampal levels determined in the previous report.

In the present study, we have also addressed the influence of kainate-induced seizures on the expression of exon-specific BDNF mRNAs in hippocampal subfields of P5 pups in comparison to adults. We observed a dramatic increase in BDNF exon I mRNA in the DG of kainate-treated adults in contrast to the restricted induction in this transcript limited to the crest of the DG in pups. The induction of BDNF exon I mRNA within the CA3 region of kainate-administered pups and adults did not greatly differ in magnitude. BDNF exon-II, III- and IV-containing transcript isoforms were all significantly upregulated by kainate in the DG, but not the CA3 and CA1, in adult animals. In contrast, kainate-treated pups showed a significant increase in BDNF exon III and IV and a trend to a significant increase in BDNF exon II mRNA expression in the CA3, but not the DG and CA1, region.

The upregulation of hippocampal BDNF mRNA following kainate-induced seizures in adult rats has been predominantly studied using probes to the BDNF coding exon V thus detecting the total pool of BDNF mRNA [4,12,18,37,44]. A few studies [27,39] have addressed the kainate-mediated regulation of exon-specific BDNF transcripts in the adult hippocampus. However, only two previous studies have examined the regulation of BDNF expression following kainate-mediated seizures in pups as compared to adults [8,20], and both these studies were carried out using probes directed at the BDNF coding exon V that does not distinguish among BDNF transcript isoforms. The present study is the

first to address the contribution of exon-specific BDNF transcripts to the regulation of BDNF mRNA observed following kainate treatment, in both pups and adults.

The two previous studies which examined the kainate-induced regulation of BDNF mRNA in pups both demonstrated a limited regulation in the developing brain. In the study by Dugich-Djordevic et al. [8], kainate resulted in a small but significant increase in the expression of BDNF in the DG at P13 but not P8, with no changes observed in the CA3 region. In contrast, the study of Kornblum et al. [20] demonstrated an increased expression of BDNF mRNA restricted to the CA3 as early as P7. The discrepancies in these two studies have been attributed to differences in treatment paradigms; however, the results of our study are in agreement with aspects of both studies. Our results indicate that as early as P5, kainate-induced seizures can enhance the expression of all BDNF exon mRNAs within the CA3 region, suggesting that all four exon promoters may contribute to kainate-mediated BDNF regulation within the CA3 region in pups. In contrast, BDNF exon I mRNA was the only transcript isoform to be induced in the DG by kainate treatment in pups, suggesting that the exon I promoter may be recruited to contribute to the restricted upregulation of BDNF mRNA in the DG of pups.

Comparing the effects of kainate on pups in the first week of life and adults more than 70 days of age, the striking difference is that all exon-specific BDNF mRNAs are upregulated by kainate in the CA3 of P5 pups in contrast to all the BDNF isoforms being increased in the DG of adults. The only BDNF transcript isoform found to be regulated in both the CA3 and DG in pups and adults was the exon I-containing BDNF mRNA, which was also the isoform that showed the highest kainate-mediated induction amongst the BDNF transcript isoforms at both ages. Even then the magnitude of induction in the DG was much lower in pups as compared to adults and restricted to the crest of the DG. The induction of BDNF transcript isoforms predominantly in the CA3 region of P5 pups is supported by previous studies indicating that kainate treatment in the first week of life results in C^{14}-deoxyglucose uptake primarily in the CA3 region [29]. The regional differences observed in the induction of BDNF transcript isoforms in neonates as compared to adults may result from differences in the magnitude and pattern of neuronal activation brought about by kainate at these two ages. The reduced response to kainate observed in pups, in particular within the DG, may be a consequence of expression of lower levels of kainate receptors in early postnatal life [2]. The other possibility is that signaling pathways and transcriptional mechanisms underlying the regulation of exon-specific BDNF expression may not have sufficiently matured in neonates. This may serve to restrict the regional distribution and extent of kainate-mediated upregulation in BDNF transcripts observed in early postnatal life. Indeed, previous studies have shown that in contrast to the effects in adults, kainate regulates expression of the transcription factor c-fos only in the CA3 region, but not in the DG, in the first week of postnatal life [30,33]. The results of our study suggest that while the regional distribution and magnitude of peak effects may be completely different in pups and adults, kainate is capable of recruiting all four BDNF promoters at both ages.

The functional significance of the regional differences in seizure-mediated induction of BDNF transcript isoforms predominantly within the CA3 in early life and in the DG in adulthood is at present unclear. However, there are several possible implications of such age-dependent differences in the pattern and magnitude of seizure-induced BDNF mRNA regulation. Previous studies indicate that the histological damage associated with seizures in neonates is less than that observed in adults [1,29]. In addition, seizure-induced aberrant sprouting of granule cell mossy fibers, and increases in subgranular zone neurogenesis, are also age-dependent with neonates exhibiting fewer reactive changes [7,21,34,46]. Although the mechanisms that underlie the decreased cell damage, reactive sprouting and neurogenesis following seizures in neonates are unknown, it is possible that the lower magnitude of induction in BDNF transcript isoforms and the restriction primarily to the CA3 region in kainate-treated pups may underlie such age-dependent differences in seizure-induced structural changes. Hippocampal CA3 cell death, mossy fiber sprouting and dentate neurogenesis have all been suggested to contribute to the seizure-induced reorganization of neuronal networks [4]. BDNF has been implicated in these long-lasting structural changes and thus thought to play a role in epileptogenesis [4,9,19,22,31,37]. The possibility exists that seizure-mediated changes in BDNF in neonates may influence both connectivity and synaptic strength during postnatal hippocampal development and thus have profound long-term consequences. Indeed, early postnatal seizures are known to contribute to long-lasting effects such as reduced seizure susceptibility, alteration in excitatory and inhibitory circuitry as demonstrated by enhanced paired-pulse inhibition in the DG, as well as impairments observed in spatial memory [13,24,35,36]. Future studies are required to address the influence of differences in BDNF transcript induction in neonates as compared to adults on the structural and functional changes implicated in epileptogenesis.

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