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Expression of cytosolic branched chain aminotransferase (BCATc) mRNA in the developing mouse brain

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Abstract

Branched-chain aminotransferase (BCAT) catalyzes the transamination of essential branched-chain amino acids (BCAAs: leucine, isoleucine and valine) with α-ketoglutarate. Through this reaction, BCAAs provide nitrogen for the synthesis of glutamate, the predominant excitatory neurotransmitter. Two BCAT isoforms have been identified: one cytosolic (BCATc) and one mitochondrial (BCATm). In adult rodents, BCATc is expressed in a wide variety of structures of the central nervous system (CNS), in neurons. So far, no data were available about the expression of BCATc in the developing CNS. Here, we analyse the expression profile of BCATc mRNA in the mouse brain from embryonic day 12.5 to adult age. BCATc mRNA gradually appears in different brain regions starting from early stages of neural development, and is maintained until adulthood. BCATc mRNA is predominantly present in the cerebral cortex, hippocampus, thalamus, ventral midbrain, raphe, cerebellum and precerebellar system. This study represents the first detailed analysis of BCATc mRNA expression in the developing mouse brain.
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Keywords: Branched chain aminoacid; Brainstem; Central nervous system; Cerebellum; Cerebral cortex; GABA; Glutamate; Habenula; Hippocampus; Interneuron; Pontine nuclei; Precerebellar system; Pyramidal neurons; Raphe; Substantia nigra; Thalamus

1. Results and discussion

Branched-chain aminotransferase (BCAT) is an important enzyme in the catabolism of the essential branched-chain amino acids (BCAAs) leucine, isoleucine and valine. BCAT catalyzes the transamination of BCAAs with α-ketoglutarate, resulting in the production of the neurotransmitter glutamate and branched-chain α-ketoacids. In this reaction, BCAAs provide nitrogen for glutamate synthesis (Yudkoff, 1997; Hutson et al., 1998; Daikhin and Yudkoff, 2000; Hutson et al., 2001). BCAT exists in two isoforms, one cytosolic (BCATc) and one mitochondrial (BCATm), BCATc being expressed at particularly high levels in the brain (Ichihara and Koyama, 1966; Ichihara, 1985; Hutson, 1988; Hutson et al., 1992; Sweatt et al., 2004; Castellano et al., 2006; Garcia-Espinosa et al., in press). In the brain, BCATc accounts for 70% of total BCAT activity, and contributes at least 30% of the nitrogen required for glutamate synthesis (Hall et al., 1993; Hutson et al., 1998; LaNoue et al., 2001). In adult rodents, BCATc is expressed in many regions of the central nervous system (CNS), including cerebral cortex, hippocampus, thalamus, cerebellum and spinal cord (Hutson et al., 2001; Sweatt et al., 2004; Madeddu et al., 2004; Castellano et al., 2006; Garcia-Espinosa et al., in press). In the CNS, BCATc is predominantly neuronal, though astrocytes have also been reported to express the BCATc protein *in vivo* after growth-factor rescue of target-deprived neurons (Madeddu et al., 2004). Moreover, it has recently been shown that during postnatal development, BCATc mRNA expression is regulated by brain-derived neurotrophic factor (BDNF) in restricted areas of the mouse brain, such as the hippocampus and

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cerebral cortex (Castellano et al., 2006). So far, no study has investigated the expression profile of BCATc during the embryonic development of the CNS. Here, we report the first detailed analysis of the expression pattern of BCATc mRNA in the developing and postnatal mouse brain.

1.1. Expression of BCATc mRNA in the embryonic mouse brain

BCATc mRNA expression in the developing brain was investigated by non radioactive *in situ* hybridisation on mouse brain sections at different embryonic stages (E12.5, E 14.5, and E16.5). At E12.5, BCATc mRNA was predominantly expressed in the central nervous system (Fig. 1A). In the brain, labelling was more intense in the telencephalon, mesencephalon and rhombencephalon (Fig. 1B). No specific labelling was detected following hybridisation with a sense probe (Fig. 1C). The expression of BCATc mRNA was particularly evident in the following areas: cerebral cortex (showing no labelling in the marginal zone and strong labelling in the ventricular zone; Fig. 1D), basal forebrain (ganglionic eminence; Table 1), ventral mesencephalon (Fig. 1E), ventricular zone of the cerebellum (Fig. 1F) and medial longitudinal fasciculus (Fig. 1G). At later stages of embryonic development (E14.5, Fig. 1H and E16.5, data not shown), BCATc mRNA continues to be expressed at elevated levels in neural structures, as compared to non-neural tissues (Fig. 1H). The diffuse labelling observed in the brain at E12.5 was maintained also at E14.5 (Fig. 1I) and E16.5 (Table 1). At these stages, BCATc mRNA labelling was observed in all the structures already labelled at E12.5, such as the ventricular zone of the

Table 1
Summary of BCATc mRNA expression in the embryonic mouse brain

Brain area	E12.5	E14.5	E16.5
Prosencephalon			
Telencephalon			
Cerebral cortex	++	++	++
Hippocampus	+	+	+
Basal forebrain	++	++	++
Diencephalon			
Epithalamus	+	+	+
Thalamus	+	+	+
Hypothalamus	+	+	+
Mesencephalon			
Ventral mesencephalon	+++	+	+
Dorsal mesencephalon	+	+	+
Rombencephalon			
Metencephalon (cerebellum)	+	++	++
Mielencephalon			
Locus coeruleus	+	+	+
Medial longitudinal fasciculus	+	+	+
Pontine nuclei	–	+++	+++
Raphe nuclei	–	+++	+++
Inferior olive	–	+++	+++

For each structure, the intensity of BCATc mRNA labelling is indicated as follows: –, not detected; +, weak (few cells, faintly labelled); ++, intermediate (many cells, moderately labelled); +++, high (many cells, intensely labelled).

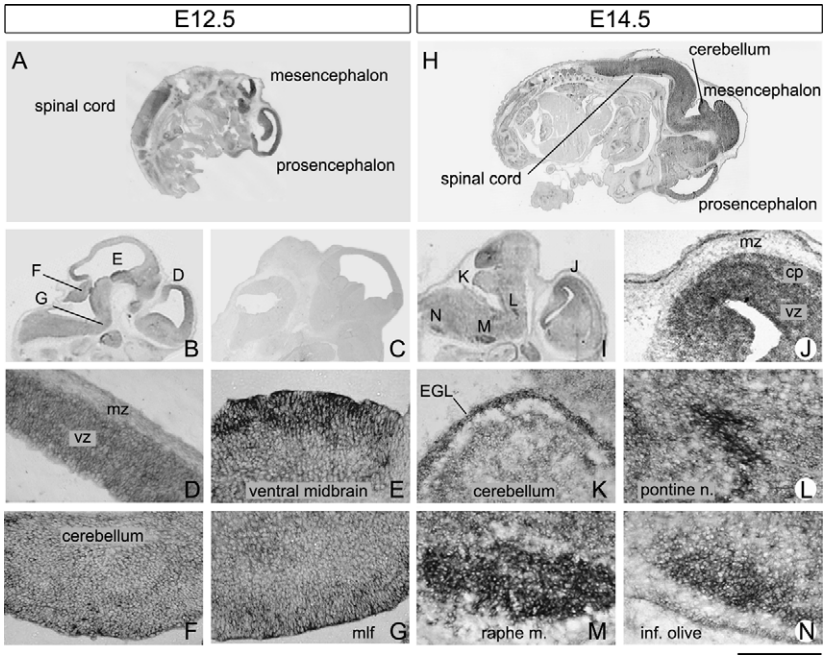

Fig. 1. Expression of BCATc mRNA in the brain at embryonic age 12.5 and 14.5. *In situ* hybridisation with antisense and sense BCATc RNA probes on sagittal sections of mouse embryos at E12.5 (A–G) and E14.5 (H–N) gestational stages. Hybridisation with a BCATc sense probe is shown in (C). (A and H) show BCATc mRNA labelling on whole embryos at E12.5 and E14.5, respectively. For embryonic age 12.5, details of areas indicated in (B) are shown in (D) cerebral cortex, (E) ventral mesencephalon, (F) ventricular zone of the cerebellum and (G) medial longitudinal fasciculus. For embryonic age 14.5, details of areas indicated in I are shown in (J) cerebral cortex, (K) cerebellum, (L) pontine nuclei, (M) raphe magnus nucleus and (N) inferior olive. *Abbreviations:* cp, cortical plate; EGL, external germinal layer of the cerebellum; inf. olive, inferior olive; mlf, medial longitudinal fasciculus; mz, marginal zone; pontine n., pontine nucleus; raphe m., raphe magnus nucleus; vz, ventricular zone; Scale bar = 4 mm (A), 3 mm (H), 1.7 mm (B, C, and I), 200 μm (D–G and J–N).

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