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Long-chain acyl-CoA hydrolase in the brain*

Minireview Article

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Summary. Long-chain acyl-CoA hydrolases are a group of enzymes that cleave acyl-CoAs into fatty acids and coenzyme A (CoA-SH). Because acyl-CoAs participate in numerous reactions encompassing lipid synthesis, energy metabolism and regulation, modulating intracellular levels of acyl-CoAs would affect cellular functions. Therefore, acyl-CoA synthetases have been intensively studied. In contrast, acyl-CoA hydrolases have been less investigated, especially in the brain despite the fact that its long-chain acyl-CoA hydrolyzing activity is much higher than that in any other organ in the body. However, recent studies have dissected the multiplicity of this class of enzymes on a genomic basis, and have allowed us to discuss their function. Here, we describe a cytosolic long-chain acyl-CoA hydrolase (referred to as BACH) that is constitutively expressed in the brain, comparing it with other acyl-CoA hydrolases found in peripheral organs that have a role in fatty acid oxidation.

Keywords: Acyl-CoA thioesterase – Long-chain fatty acyl-CoA – Lipid metabolism – Neuron

Introduction

Activation of fatty acids to the corresponding acyl-CoA thioesters is an initial reaction in cellular fatty acid metabolism. Therefore, acyl-CoAs are primary substrates for fatty acid degradation and lipid synthesis, and the source of signaling molecules like ceramide and diacylglycerol (Faergeman and Knudsen, 1997; Watkins, 1997). Acyl-CoAs also serve as modulators in various cellular mechanisms including ion fluxes, vesicle trafficking, protein phosphorylation and gene expression (Faergeman and Knudsen, 1997; Hertz et al., 1998; Elholm et al., 2001). Protein acylation also anchors proteins to specific membranes and enables them to function correctly (Mumby, 1997). Thus, modulating intracellular levels of acyl-CoAs would affect cellular functions. In view of this, acyl-CoA synthetases (fatty acid-CoA ligases) have been intensively studied (Watkins, 1997). Some of these enzyme types are highly expressed in the brain, and their defects have indeed been implicated as causes of abnormal brain development and neurodegeneration, as in X-linked mental retardation (Meloni et al., 2002) and X-linked adrenoleukodystrophy (Moser et al., 2000). On the contrary, acyl-CoA hydrolases that cleave acyl-CoAs into fatty acids and CoA-SH have been less investigated, especially in the brain despite the fact that its long-chain acyl-CoA hydrolyzing activity is much higher than that in any other organ in the body (Kurooka et al., 1972; Katoh et al., 1987; Kuramochi et al., 2002a). However, recent studies have dissected multiplicity of this class of enzymes on a genomic basis, and allowed us to discuss their function. In this article, we describe a long-chain acyl-CoA hydrolase that is highly expressed in the brain, comparing it with other acyl-CoA hydrolases found in peripheral organs with a role related to fatty acid oxidation.

Multiplicity of long-chain acyl-CoA hydrolases

Long-chain acyl-CoA hydrolases or thioesterases (EC 3.1.2.2) are a group of enzymes that catalyze the hydrolysis of fatty acyl-CoA thioesters into free fatty acids and CoA-SH (reviewed by Hunt and Alexson, 2002). The enzyme activity is ubiquitously found in organisms and cell types and in most cellular compartments, although in

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some cases, it is often accounted for by microsomal carboxylesterases with multi-substrate specificities. The potency of acyl-CoA hydrolases may be a mechanism that regulates intracellular levels of acyl-CoAs, free fatty acids and CoA-SH to affect various cellular mechanisms and functions, because acyl-CoAs participate in a large number of reactions, including lipid synthesis, energy metabolism and regulation, as described above. However, the physiological functions of acyl-CoA hydrolases have not been fully established. In previous studies, we and others have identified novel members of long-chain acyl-CoA hydrolases in rats, mice and humans by means of protein purification and molecular cloning. These enzymes, tentatively termed type-I and type-II acyl-CoA thioesterases according to the nomenclature proposed by Alexson's group (Hunt and Alexson, 2002), have been characterized as highly specific in hydrolyzing fatty acyl-CoAs, and have been implicated in lipid metabolism (Miyazawa et al., 1981; Kawashima et al., 1982; Yamada et al., 1994, 1996; Broustas and Hajra, 1995; Svensson et al., 1995).

Acyl-CoA hydrolases involved in fatty acid oxidation

To date, it has been shown that mouse type-I acyl-CoA thioesterases comprise four isoforms with cytosolic, mitochondrial and peroxisomal localizations, and form a highly homologous multi-gene family with their human orthologs being located within a very narrow region of chromosome 14 as a gene cluster (Hunt et al., 1999). In rats, mitochondrial (MTE-I) and cytosolic (CTE-I) isoforms are found in a wide variety of tissues in the body, primarily localized in epithelia, and mainly in tissues closely related to fatty acid oxidation (Kuramochi et al., 2002b). For example, kidney contain high levels of both enzymes primarily in the proximal tubules, where a large energy demand is expected due to the presence of highly active transporters and fatty acids represent a major fuel (Schmid et al., 1980; Le Hir and Dubach, 1982). MTE-I and CTE-I are also markedly induced in the liver of diabetic and fasted rats (Hunt et al., 1999, 2000; Yamada et al., 2003). In a situation of enhanced fatty acid oxidation due to stimulated fatty acid mobilization from the adipose tissues in liver, MTE-I may help in maintaining optimal conditions for mitochondrial β-oxidation by hydrolyzing excessive acyl-CoAs taken up into this organelle to supply sufficient CoA-SH to β-oxidation enzymes (Svensson et al., 1998). In the cytosol, CTE-I may support ω-oxidation by hydrolyzing acyl-CoAs into free fatty acids that can be ω-hydroxylated and subsequently oxidized to dicarboxylic acids (Huhtinen et al., 2002). This may also be the case in hepatic adaptation of lipid metabolism after feeding on a high-fat diet. Therefore, induction of MTE-I and CTE-I represents an adaptive response to fatty acid overload in the liver.

In addition, to provide an effective pathway for fatty acid catabolism, gene expression of MTE-I and CTE-I seems to be regulated by peroxisome proliferator-activated receptor (PPARα) in a manner synchronized with that involved in β-oxidation and ω-oxidation (Hunt et al., 2000). This mechanism has been documented by co-induction of relevant enzymes in liver after treatment with peroxisome proliferators, such as fibrate-class of hypolipidemic drugs (Kawashima et al., 1982; Yamada et al., 1994, 1998; Svensson et al., 1995, 1998; Kuramochi et al., 2002b). Recent findings on PPARα-mediated regulation of MTE-I and uncoupling protein (UCP3) gene expression in muscles are also consistent with the coordinated regulation of MTE-I to promote fatty acid oxidation by acting in concert with UCP3 in mitochondria (Stavinoha et al., 2004). Thus, type-I acyl-CoA thioesterases, also including peroxisomal PTE-I (Westin et al., 2004), likely play an auxiliary role in fatty acid oxidation in response to increased availability of fatty acids.

Brain acyl-CoA hydrolase (BACH)

Type-II acyl-CoA thioesterases include mitochondrial and cytosolic isoforms (MTE-II and CTE-II, respectively) and are derived from a single gene referred to as *BACH* (Yamada et al., 2002), of which the structural organization is depicted in Fig. 1. The human BACH gene spans about 130 kb, mapped to 1p36.31–p36.11, and comprises thirteen exons, of which the four first exons (1a–1d) can be used, and three patterns of splicing occur at exon X located between exons 7 and 8, giving rise theoretically to twelve isoforms through a mechanism of alternative use of exons.

In practice, full-length cDNAs for six kinds of BACH isoforms were cloned from human brain RNAs (Yamada et al., 2002). These clones had unique sequences derived from the respective exon 1's and shared the same sequence corresponding to exons 2–9, with or without exon X-derived sequences. When expressed in bacteria, cDNAs for four out of six BACH isoforms generated acyl-CoA hydrolase activity with similar chain-length specificities, whereas two cDNAs with exon X-derived insertions did not, because of premature stop codons created by frameshift. Real-time quantitative RT-PCR revealed that among the isoforms, the one (BACHa) previously cloned as

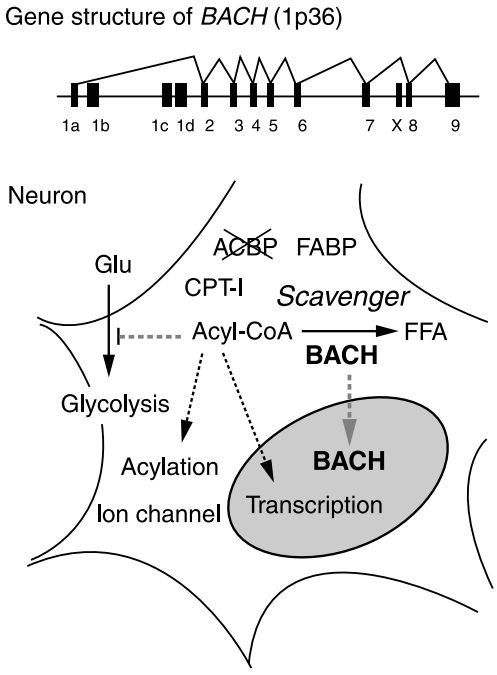

Fig. 1. Structural organization of the human BACH gene (Top). Exons are depicted as closed boxes with an associated number, and introns and flanking regions by solid lines. Possible roles of BACH in neurons (Bottom). See text for detail. *ACBP*, acyl-CoA binding protein; *CPT-1*, carnitine palmitoyltransferase-1; *FABP*, fatty acid binding protein; *FFA*, free fatty acid; *Glu*, glucose

BACH (Yamada et al., 1997, 1999; Kuramochi et al., 2002a), CTE-II (Engberg et al., 1997) or ACT (Broustas et al., 1996) is exclusively expressed in the brain. Of the four isoforms with enzyme activity, another one (BACHb) corresponded to MTE-II (Svensson et al., 1995) or LACH1 (Yamada et al., 1997), as demonstrated by mitochondrial localization of its recombinant protein expressed in Neuro-2a cells with a green fluorescent protein (GFP)-tag. BACHa (CTE-II) and BACHb (MTE-II) are induced in the liver of rats treated with peroxisome proliferators (Miyazawa et al., 1981; Yamada et al., 1994, 1997; Svensson et al., 1995; Engberg et al., 1997). However, this phenomenon appears specific to rats, because it has never been observed anywhere else, even in mice, at least with respect to BACHa (Kawashima et al., 1983). Interestingly, BACHa contains a nuclear localization signal (NLS) in its primary structure. This signal is functional, because GFP-fusion of the NLS polypeptide expressed in Neuro-2a cells was exclusively localized to the nucleus, although that of entire BACHa polypeptide was cytosolic. Moreover, immunohistochemistry of brain sections suggested that BACH exists within the nucleus as well as in the cytosol of some neurons, raising the possibility of nuclear translocation of this enzyme from the cytosol (Yamada et al., 2002). Thus, the BACH gene can express long-chain acyl-CoA hydrolase activity in multiple intracellular compartments by generating isoforms with differential localization signals to affect various cellular functions that involve acyl-CoAs.

The BACH gene is highly conserved between humans and mice, and its expression pattern is also the same in brain where BACHa isoform is solely expressed (Yamada et al., 1999, 2002; Kuramochi et al., 2002a). BACH (refers to BACHa isoform otherwise noted) is a soluble protein with a molecular mass of 110 kDa, composed of a 43-kDa subunit with 338 amino acids. The amino acid sequences of human and mouse homologs are 96% identical to each other, and the corresponding value between the mouse and rat homologs reaches 99%. BACH is highly specific for the hydrolysis of acyl-CoA and can not act as an acyltransferase, transacylase or O-acyl hydrolase (Broustas and Hajra, 1995). However, its chain-length specificity is relatively broad, as this enzyme hydrolyzes acyl-CoAs with carbon number of C6–20 or more and those with C8–18 are good substrates. Unsaturated fatty acyl-CoAs, like oleoyl-CoA (C18:1), are also efficiently hydrolyzed (Yamada et al., 1994, 1996, 1999; Broustas and Hajra, 1995). The acyl-CoA hydrolase activity exhibited by BACH is very high. For example, with palmitoyl-CoA (C16) as the substrate, the maximal velocity (Vmax) of the enzyme reaction is about 300 μmole/min/mg, a value two orders of magnitude higher than that found with carboxylesterases or type-I acyl-CoA thioesterases with similar affinities (Km values of 5–6 μM) for the substrate (Yamada et al., 1994, 1996, 1999).

While long-chain acyl-CoA hydrolase activity is widely distributed in mouse tissues, it is marked in brain, being consistent with BACH almost exclusively found there (Kuramochi et al., 2002a). In our estimation using an anti-BACH antibody, 86% of the palmitoyl-CoA hydrolyzing activity was recovered in the cytosol after centrifugation of mouse brain homogenates, and 95% of the cytosolic activity was attributed to BACH. Similar results were obtained with human and rat brains (Yamada et al., 1996, 1999). Moreover, immunohistochemistry in rats and mice demonstrated neuronal localization of BACH both in the central and peripheral nervous systems (Yamada et al., 1996; Kuramochi et al., 2002a). Immunoreactivity was found all over the brain, and clear staining was observed in certain types of neurons including the pyramidal cells of the cerebral cortex, Purkinje and granule cells in the cerebellum, and brainstem neurons within the locus

ceruleus and dorsal motor nucleus of the vagus. Immunoreactivity was also seen in peripheral nerves such as plexuses in the rectum and ganglia in the submaxillary gland. In cultured neurons, BACH reactivity was detected in the cell body and neurites. The neuronal distribution of BACH was also confirmed in human brain sections (Yamada et al., 2002). We found no evidence of the presence of BACH in glia.

Recently, we performed a developmental analysis of BACH gene expression (Yamada et al., 2004). BACH protein (43 kDa) was detected in mouse brain as early as embryonic day 11.5 (E11.5). At that time point, BACH protein level was low and remained low until E12.5, but promptly increased to reach a peak 7 days after birth. Thereafter, it declined somewhat and reached a steady-state level in adulthood. These changes in BACH expression were approximately reflected in the palmitoyl-CoA hydrolyzing activity in the developing mouse brain, and the time course was quite similar to that of microtubule-associated protein 2 (MAP2) expression, a differentiated neuron marker. In immunohistochemistry of E14.5 embryo brains, cells expressing BACH almost coincided with cells committed to neuronal lineage, which expressed MAP2 but not nestin, a marker for neural stem cells. These results indicate that BACH expression is induced during embryogenesis in association with neuronal differentiation, and persists after terminal differentiation in neurons at postnatal stages, resulting in constitutive high expression of BACH in the adult brain in a neuron-specific manner.

Possible roles of BACH in neurons

Since its first description in the literature in 1958, it has been well documented that there is a markedly high level of long-chain acyl-CoA hydrolase activity in the brain of mammals (Vignais and Zabin, 1958; Srere et al., 1959; Anderson and Erwin, 1971; Kurooka et al., 1972; Knauer, 1979), suggesting some specific role of the enzyme activity in this organ. Following this observation, recent work identified and characterized BACH as the responsible enzyme, as described above. However, its physiological significance is still elusive. Because of its expression in almost all brain regions harboring mature neurons (Yamada et al., 1996; Kuramochi et al., 2002a), BACH may be involved in a general aspect of neuronal functions. In this context, type-I acyl-CoA thioesterases are suggested to play a role associated with fatty acid oxidation in liver and kidneys etc., as described above. However, astrocytes are the ones effectively using fatty acids as an oxidative fuel in brain (Edmond et al., 1987), suggesting that BACH may not be essential for energy metabolism using lipid fuel in brain.

We favor the hypothesis that BACH may serve as a potent scavenger of cytosolic free long-chain acyl-CoAs. These molecules were reported to directly inhibit certain glycolytic enzymes, such as hexokinase in extracerebral tissues (Faergeman and Knudsen, 1997; Thompson and Cooney, 2000), and thus accumulation of free long-chain acyl-CoAs in the cytosol could significantly influence cell viability if such an inhibition occurred in neurons that utilize glucose as almost their sole energy source. Moreover, these acyl-CoAs can act as regulatory molecules, as exemplified by protein kinase C activation (Nesher and Boneh, 1994), calcium release (Fitzsimmons et al., 1997), and ATP-sensitive potassium channel activation (Gribble et al., 1998), but can also be cytotoxic at high concentrations due to their detergent property (Boylan and Hamilton, 1992), as well as substrates for lipid metabolism. In general, cytosolic long-chain acyl-CoAs are specifically bound to acyl-CoA binding protein (ACBP) with high affinity so that they can be protected from hydrolysis by acyl-CoA hydrolases (Faergeman and Knudsen, 1997). They are also converted to acyl-carnitine by carnitine palmitoyltransferase (CPT-I), resulting in a very low concentration of free long-chain acyl-CoAs in the cytosol (Faergeman and Knudsen, 1997; Zammit, 1999). In addition to these enzymes, the potent hydrolytic activity of BACH would provide another mechanism to maintain acyl-CoA levels, ensuring the turn-off of the regulatory acyl-CoA signal and prevention of cytotoxicity and uncontrolled substrate supply caused by increased levels of free long-chain acyl-CoAs. Recently, an immunohistochemical study in mice showed a lack of ACBP in neurons (Yanase et al., 2002). This suggests an important contribution of BACH as an acyl-CoA scavenger in neurons, that may in turn explain the selective expression of BACH in this cell type.

Of interest, intraneuronal levels of long-chain acyl-CoAs are proposed to represent a key signal in a central nutrient-sensing that constitutes a mechanism coupling energy balance with glucose homeostasis (Pocai et al., 2005). Using an animal model, it was shown that central administration of either, fatty-acid synthase inhibitors (Loftus et al., 2000), or CPT-1 antagonists (Obici et al., 2003), or oleic acid (Obici et al., 2002) is sufficient to substantially diminish food intake and hepatic glucose production, and postulated that a common effect of these central anorectic agents is to increase cellular concentration of long-chain acyl-CoAs within selective brainstem

neurons. Although it remains to be determined whether circulating lipids can generate a similar increase in neuronal acyl-CoAs, the access of circulating free fatty acids to the central nervous system is generally proportional to their plasma concentration (Miller et al., 1987; Rapoport, 1996). Therefore, neuronal lipid metabolism may represent a primary biochemical sensor for nutrient availability to exert a negative feedback on food intake and endogenous glucose production via neural circuitry that requires the activation of ATP-sensitive potassium channels (Pocai et al., 2005). It will be of interest to examine the possible role of BACH in this central nutrient-sensing mechanism.

Long-chain acyl-CoAs were reported to play a role in synaptic vesicle formation (Schmidt et al., 1999), long-term potentiation in the hippocampus (Zhang et al., 2000), and inhibition of dopamine sulfotransferase (Tulik et al., 2002), on which BACH might possibly have an influence.

In summary, BACH has been identified as an enzyme responsible for the well-documented long-chain acyl-CoA hydrolyzing activity in the brain and characterized in various aspects. The highly conserved nature of the BACH gene has also been revealed. However, before the real function of BACH can be established, many more studies are required. For that purpose, manipulation of BACH gene expression in animal models or phenotypic analysis of human diseases associated with this enzyme will provide a useful approach for investigation. In this context, a recent proteomics analysis of epileptic brain specimens also represents a promising approach, that pointed out alterations in BACH protein from the patients' hippocampus (Yang et al., 2004).

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