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BRAIN RESEARCH REVIEWS

Review

Uridine and cytidine in the brain: Their transport and utilization

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ABSTRACT

The pyrimidines cytidine (as CTP) and uridine (which is converted to UTP and then CTP) contribute to brain phosphatidylcholine and phosphatidylethanolamine synthesis via the Kennedy pathway. Their uptake into brain from the circulation is initiated by nucleoside transporters located at the blood–brain barrier (BBB), and the rate at which uptake occurs is a major factor determining phosphatide synthesis. Two such transporters have been described: a low-affinity equilibrative system and a high-affinity concentrative system. It is unlikely that the low-affinity transporter contributes to brain uridine or cytidine uptake except when plasma concentrations of these compounds are increased several-fold experimentally. CNT2 proteins, the high-affinity transporters for purines like adenosine as well as for uridine, have been found in cells comprising the BBB of rats. However, to date, no comparable high-affinity carrier protein for cytidine, such as CNT1, has been detected at this location. Thus, uridine may be more available to brain than cytidine and may be the major precursor in brain for both the salvage pathway of pyrimidine nucleotides and the Kennedy pathway of phosphatide synthesis. This recognition may bear on the effects of cytidine or uridine sources in neurodegenerative diseases.

Contents

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1. Introduction

The circulating pyrimidines uridine and cytidine, besides being incorporated into nucleic acids, can serve as substrates for the salvage pathway of pyrimidine nucleotide synthesis; as precursors of the cytidine triphosphate (CTP) needed in the phosphatidylcholine (PC) and phosphatidylethanolamine (PE) biosynthetic pathway (Kennedy and Weiss, 1956); and as precursors for the UDP (uridine diphosphate) and UTP (uridine triphosphate) that activate brain P2Y receptors (von Kugelgen, 2006) and that promote brain glycogen synthesis via UDP-glucose (Brown, 2004). In humans, the predominant circulating pyrimidine is uridine (Wurtman et al., 2000); in rats, it is cytidine (Traut, 1994); these variations probably reflect the species differences in cytidine deaminase, the enzyme that converts cytidine to uridine in the body. The transports of these pyrimidines into the brain's extracellular fluid, and then into neurons and glia, are essential prerequisites for these nucleosides to be utilized in brain. This review describes the mechanisms currently believed to mediate their passage across the blood–brain barrier (BBB) and then into brain cells. It also considers the biochemical consequences of changing brain uridine and cytidine levels, and related therapeutic implications.

CDP-choline is an endogenous intermediate which is produced in the rate-limiting step of PC biosynthesis via the Kennedy pathway (Kennedy and Weiss, 1956) (Fig. 1). Thus, CDP-choline has been extensively studied for its role in neuronal membrane synthesis. Exogenously administered CDP-choline is metabolized to cytidine and choline in rats (Weiss, 1995), while it is metabolized to uridine and choline in humans (Wurtman et al., 2000). Thus, besides choline, cytidine and uridine have attracted attention as precursors for endogenous CDP-choline production. An efficient mechanism mediating the brain uptake of circulating cytidine has not yet been demonstrated. When double-labeled CDP-choline was administered orally to rats, brain cytidine radioactivity peaking 4–6 h after the labeled CDP-choline was very low compared with that in liver (i.e., 0.2% vs. 60% of administered dose for brain and liver, respectively [Galletti et al., 1991]). Cytidine administered intracerebroventricularly (i.c.v.) does enter the brain (Trovarelli et al., 1982), but uptake via this route bypasses BBB transport.

On the other hand, the brain is known to take up circulating uridine. This uptake was initially demonstrated in the early 1970s (Hogans et al., 1971). Subsequently, Cornford and Oldendorf (1975), using a single injection method, showed that adenine, adenosine, guanosine, inosine and uridine all are able to cross the rat BBB, while cytidine, thymidine and their respective bases are not. Further studies on nucleoside transport suggested that nucleoside transporters could be classified based on their sensitivity to the nucleoside analog S-(4-nitrobenzyl)-6-thioinosine (NBTI) into two groups as NBTI-sensitive (*es*) or NBTI-insensitive (*ei*) (Belt, 1983). A few years later, the finding of a totally different type of nucleoside transporter family in mouse intestinal epithelial cells (Vijayalakshmi and Belt, 1988) gave rise to a new classification of nucleoside transporters, i.e., into equilibrative (Na^+-independent, low-affinity) and concentrative (Na^+-dependent, high-affinity) transporter families. The properties and substrate specificity of each family have been reviewed in Table 1. Detailed information can be found elsewhere (Baldwin et al., 2004; Gray et al., 2004; Kong et al., 2004; Podgorska et al., 2005).

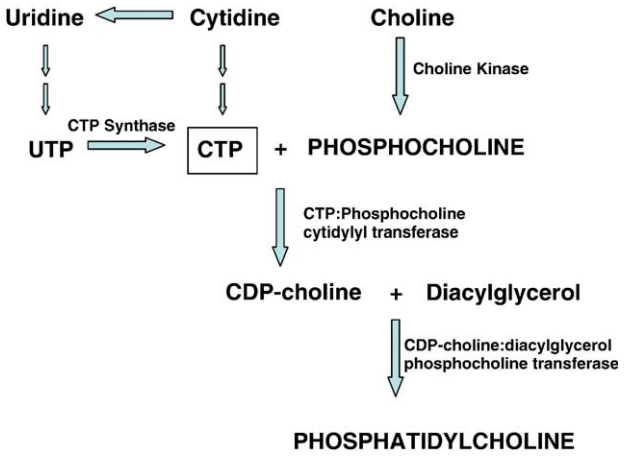

Fig. 1 – Phosphatidylcholine (PC) biosynthesis via the Kennedy pathway. In rats, plasma cytidine is the major circulating pyrimidine, however in gerbils and humans, the primary circulating pyrimidine is uridine. Only small amounts of circulating cytidine are converted to brain CTP, since the rat blood–brain barrier (BBB) lacks a high-affinity transporter for cytidine; uridine, in contrast, readily enters the brain via a high-affinity transporter (CNT2) yielding UTP which is then converted to CTP by CTP synthase. This CTP reacts with phosphocholine to form endogenous CDP-choline, which than combines with diacylglycerol (DAG) to form PC.

Recent studies employing expression cloning and reverse transcriptase-PCR (RT-PCR) methods revealed the expression of a high-affinity nucleoside transporter (CNT2) at the rat BBB for purines like adenosine, and the pyrimidine uridine (Li et al., 2001; Redzic et al., 2005), but not for cytidine. Since BBB transport is the major determinant of brain uptake of most circulating compounds (Pardridge, 2001), this recent finding may open new avenues for exploring the possible effects of cytidine or uridine sources in neurodegenerative disorders like Alzheimer's disease.

2. Transport of cytidine and uridine across the BBB

Circulating cytidine and uridine can both be transported across the BBB by equilibrative transporters. Moreover, a concentrative system, as mentioned above, has also recently been shown to mediate BBB uridine transport. Equilibrative transport proteins (ENT, SLC29 family) exhibit characteristics of low-affinity nucleoside transport with K_m values for their substrates in the high micromolar range (100–800 μM; Pastor-Anglada et al., 1998). Two such transporters, ENT1 and ENT2, have been cloned in rat (Redzic et al., 2005) and mouse (Murakami et al., 2005) BBB. Both ENT1 and ENT2 can