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Lactate and Ketone Bodies Act as Energy Substrates as Well as Signal Molecules in the Brain

Shinichi Takahashi

Abstract

Astroglia or astrocytes, the most abundant cells in the brain, are interposed between neuronal synapses and the microvasculature in the brain's gray matter. This unique anatomical location allows astroglia to play pivotal roles in brain metabolism as well as in the regulation of cerebral blood flow. In particular, astroglial cellular metabolic compartmentation exerts supportive roles in dedicating neurons to the generation of action potentials and protects neurons against the oxidative stress associated with their high energy consumption. Key products of astroglia include lactate and ketone bodies (beta-hydroxybutyrate and acetoacetate), which can also be produced avidly by muscle and liver, respectively. Therefore, brain cells, skeletal muscles, and hepatocytes constitute a metabolic compartmentation in the whole body. In this chapter, I will focus on brain cells, especially astroglia, since the impairment of normal astroglial function can lead to numerous neurological disorders including stroke, neurodegenerative diseases, and neuro-immunological diseases. I will also discuss the metabolic responses of brain cells in terms of food consumption and exercise. A better understanding of the astroglial metabolic response is expected to lead to the development of novel therapeutic strategies for diverse neurological diseases.

Keywords: astrocyte, astroglia, brain-derived neurotrophic factor, beta-hydroxybutyrate, fatty acids, glucose

1. Introduction

“Eating”, especially glucose ingestion is essential for brain function. When we get tired either physically or mentally, we may want “sweet stuff”. Some people prefer “fatty food”. These unconscious impulses imply fundamental roles of glucose and fatty acid in the brain. The human brain is a complex, organized organ consisting of numerous cell types including neurons and glial cells [1, 2]. In addition, the microvasculature, which supplies oxygen and glucose, is also an essential component [3]. The human adult brain weighs 1.4 kg, or approximately 2% of the body weight, and consumes 20% of the total oxygen consumption and 25% of the glucose consumption in the body (**Figure 1**) [4, 5]. Brain function mainly consists of intellectual information processing, which is based on the generation of action potentials resulting from ionic flux across the cellular membrane. The ratio of the cerebral metabolic rate of oxygen (CMR_{oxy}) to glucose (CMR_{glc}) consumption

Figure 1.
Cerebral metabolic rate of glucose (CMR_{glc}) and oxygen (CMR_{oxy}) in human adults (adapted from [4]).

is approximately 6, implying the complete oxidation of one molecule of glucose (6 carbon molecules) for every 6 molecules of oxygen, producing CO_2 and H_2O (**Figure 1**) [4, 5]. The first step in glucose metabolism is glycolysis, which generates 2 ATPs; pyruvate/lactate is the end-product of glycolysis, and this product then enters the tricarboxylic acid (TCA) cycle, where ATP is produced more efficiently (resulting in 36 ATPs). Continuous ATP production is essential to generate action potentials, maintaining consciousness as well as intellectual function. Surprisingly, however, ATP production in the brain is solely dependent on glucose and oxygen as energy substrates [4, 5]. Moreover, these essential energy substrates must be supplied from outside of the brain through the microvasculature, since there is virtually no storage of glucose or oxygen in the brain. As a result, even a short period of cessation in cerebral blood flow (CBF) induces an immediate impairment of brain function [6]. Longer periods of ischemia cause irreversible damage to brain cells, making the restoration of function in stroke patients difficult even after vigorous rehabilitation [6, 7].

Regarding the maintenance and restoration of brain function, the topic of synaptic plasticity is essential. The theoretical basis of the beneficial effects of physical exercise on brain function relies on the facilitation of synaptic transmission and plasticity. Brain-derived neurotrophic factor (BDNF) plays a pivotal role in maintaining the neural network, improving its function, and restoring the network after damage [8, 9]. BDNF is a neurotrophic factor that was identified in the pig brain for the first time in 1982 [9]. BDNF, which is produced in both neurons and glial cells, improves a wide variety of neuronal functions including both motor functions and memory [8, 9]. Physical exercise does, indeed, improve not only motor function, but also mental function [10–12]. Unfortunately, however, the exact mechanism by which physical exercise induces BDNF production in the brain has not yet been elucidated. Recently, two nutrient molecules that are closely related to brain energy metabolism have become points of focus: lactate [13, 14] and beta-hydroxybutyrate (BHB) [15, 16]. The former is an end-product of glycolysis, and the latter is a type of ketone body, which are metabolites of fatty acid produced through beta-oxidation. Importantly, the concentrations of both lactate and BHB have been widely recognized as being elevated after exercise as a result of increases in their production by skeletal muscle and in the liver, respectively. Furthermore, both lactate and BHB are transported into the brain via monocarboxylate transporters (MCTs) (**Figure 2**) [17]. Therefore, lactate and BHB are also cable of acting as signal molecules resulting in BDNF production in the brain.

Figure 2.
Physical activity, brain, muscle, liver, and BDNF: hypothetical model 1. BDNF, brain-derived neurotrophic factor; MCT1, monocarboxylate transporter 1 (expressed on brain microvessels).

As described above, brain energy metabolism is solely dependent on exogenous glucose and oxygen supplied from outside the brain under normal physiological conditions [4, 5]. Importantly, however, it has also long been known that exogenous lactate and BHB can fuel the brain as alternative energy substrates under non-physiological conditions such as starvation, insulin-resistance and so on [4, 5]. Lactate enters the TCA cycle of the neurons after the conversion of acetyl-CoA by the pyruvate dehydrogenase complex (PDHC), while BHB can enter the TCA cycle directly without the action of PDHC (**Figure 3**) [4, 5]. These mechanisms imply that the exercise-induced production of lactate and BHB provides (1) energy substrates for the short-term maintenance of brain function, and (2) signal molecules capable of inducing BDNF production in the brain for the long-term maintenance of brain plasticity.

Figure 3.
Transportation and metabolic pathway of lactate and ketone bodies (β -hydroxybutyrate and acetoacetate) into neural cells. MCT, monocarboxylate transporter; Glut, glucose transporter; TCA, tricarboxylic acid; PDHC, pyruvate dehydrogenase complex.

Figure 4. Physical activity, brain (neurons and glial cells), muscle, liver, and BDNF: hypothetical model 2. BDNF, brain-derived neurotrophic factor; MCT2, monocarboxylate transporter 2 (expressed on neurons), MCT4, monocarboxylate transporter 4 (expressed on astroglia).

The brain, muscle, and liver therefore compose a metabolic network that is linked through physical exercise. Of note, physical exercise (voluntary movement) is initiated by neuronal excitation (**Figure 2**) [4, 5]. Generally, the functional activation of the brain increases both local CMR_{glc} and local CMR_{oxy} to produce more ATPs. Under normal resting conditions, neither lactate nor BHB is present in the blood in sufficient quantities to be transported into the brain because of the slow transportation kinetics of MCTs [4, 5]. As a result, their roles as energy substrates for the brain seem to be limited. Importantly, however, the brain itself, or more exactly its astroglia, can produce both lactate and BHB upon neuronal excitation (**Figure 4**) [3–5]. Our research has focused on the metabolic compartmentalization between neurons and glial cells [18–27], revealing that astrocytes produce both lactate and BHB, both of which can fuel neurons as energy substrates, via processes that are coupled with neuronal excitation [3]. Accumulating evidence supporting the actions of exogenous lactate and BHB as signal molecules that induce BDNF converge in this intracerebral metabolic compartment between neurons and astrocytes, where astrocyte-derived lactate and BHB support neuronal function in terms of both energy metabolism and synaptic plasticity [3].

2. Sources and roles of exercise-induced lactate and ketone bodies in the brain

Physical activity is known to elevate lactate levels in the blood [13, 14]. Since physical activities are beneficial for the maintenance of both mental and physical health, an exploration of the mechanisms by which physical exercise improves neuronal function is an important target. Energetically, human brain function is solely dependent on the oxidative metabolism of glucose [4, 5]. Glucose is continuously supplied by the blood stream, since virtually no glucose storage exists in the brain. Besides the brain, only the testis is known to rely on glucose as an energy substrate [4, 5].

Glucose in the blood is taken up by glucose transporter 1 (Glut1) in the endothelium of brain microvessels [3–5, 17]. In addition to this glucose transporter, MCTs expressed in the brain microvessels allow lactate and ketone bodies

(especially BHB) to cross the blood–brain barrier (BBB) [3–5, 17]. Neural cells (neurons and glia) are thus able to take up glucose, lactate, and BHB via glucose transporters or MCTs (**Figure 2**) [17]. Once lactate or BHB is transported into the brain cells, they enter the TCA cycle to act as energy substrates, similar to glucose (**Figure 3**). Although neither lactate nor BHB is an efficient energy substrate because of the slow transportation kinetics of MCTs, elevations in their blood concentrations allow them to act as energy sources supplied externally from the brain [3–5]. The concentrations of both lactate and BHB do, indeed, increase after physical exercise [28, 29]. The sources of the elevated lactate and BHB levels in the blood after physical activity are the skeletal muscles and liver, respectively [3–5]. Under starvation and insulin-resistance in diabetic patients, glucose availability in the peripheral tissue is limited, and BHB can fuel brain function in the place of glucose.

In addition to their roles as energy substrates, both lactate and BHB can improve brain function through synaptic plasticity. Ample evidence supports BDNF being a key molecule in the induction of neuronal plasticity [8, 9]. BDNF is a member of the neurotrophin family and is produced in neurons as well as glial cells [8, 9]. BDNF promotes neurite outgrowth, facilitates synaptic transmission, and regenerates the neuronal network. Recent evidence suggests that both lactate and BHB, which are produced outside the brain during physical exercise, act as signal molecules in the brain after crossing the BBB [13–16]. Lactate induces BDNF expression, and this action of lactate is dependent on the activation of Sirtuin1 deacetylase. Silent information regulator 1 (SIRT1) increases the levels of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) and the secreted molecule fibronectin type III domain-containing protein 5 (FNDC5), which are known to mediate BDNF expression [13, 14]. In contrast, BHB induces BDNF expression by acting as a direct Class I histone deacetylase (HDAC) inhibitor. By inhibiting HDAC2 and HDAC3 and by preventing their recruitment to BDNF promoter I, BHB induces BDNF expression [15, 16].

3. Lactate production and consumption in the brain

In addition to skeletal muscles, numerous cells in the body generate lactate. Especially under a hypoxic/anoxic state, virtually all cell types generate lactate through glycolysis, since the further oxidation of lactate in the mitochondrial TCA cycle is inhibited because of oxygen unavailability [3–5]. Importantly, even under a sufficient supply of oxygen, lactate production can occur (aerobic glycolysis). Although brain function is dependent on the complete oxidation of glucose, cellular differences in the cell types should be noted. In fact, astroglia seem to be more glycolysis-dependent, compared with neurons (**Figure 5**) [3, 23]. Astroglia exhibit normal mitochondrial function and are capable of oxidizing glucose as well as lactate/pyruvate in mitochondria (**Figures 6–8**), albeit lactate/pyruvate does not seem to be an ideal substrate [3, 23].

Astroglial endfeet envelope brain microvessels as well as synapses (**Figure 9**) [30–32]. This anatomical location of astroglia seems to be suitable for the direct uptake of glucose from the microvessels [3]. Glucose is metabolized glycolytically in the astroglial cytosol, generating lactate/pyruvate (**Figure 9**). In contrast to neurons, however, ATP consumption by astroglia is much smaller than that by neurons, since astroglia do not generate action potentials. In fact, approximately one half of the total neuronal ATP consumption reflects Na⁺,K⁺-ATPase activity, which restores and maintains the ionic gradient across the cell membrane to maintain the generation of action potentials [4, 5]. Astroglial Na⁺,K⁺-ATPase also plays

Figure 5. Glucose consumption and lactate production measured directly in culture medium for rat astroglia and neurons (adapted from [23]).

Figure 6. Competition assay 1: [¹⁴C]glucose oxidation is inhibited by lactate by approximately half in neurons but not in astroglia (adapted from [23]).

a role in maintaining the ionic gradient, and this helps astroglia to take up glutamate released into the synaptic cleft (**Figure 9**) [3, 18, 33]. Glutamate is the most widely distributed excitatory transmitter, and primary motor neurons in the motor cortex release glutamate, which in turn activates secondary motor neurons in the spinal cord to induce muscle contraction. Whether glutamate re-uptake stimulates astroglial CMR_{glc} and CMR_{oxy} remains controversial [3, 18, 33–53]. In an in vitro culture model, at least, the application of glutamate increased glucose consumption (**Figure 10**) as well as lactate production (**Figure 11**), suggesting the activation of glycolysis in an CMR_{oxy}-independent manner [3, 18, 33].

Figure 7.
Competition assay 2: $[^{14}\text{C}]$ lactate oxidation is somewhat inhibited by glucose in neurons but is markedly inhibited in astroglia (adapted from [23]).

Figure 8.
Competition assay 3: $[1-^{14}\text{C}]$ pyruvate oxidation is somewhat inhibited by glucose in neurons.

4. Primary astroglia from rodent brain and human iPS cell-derived astroglia

Classically, cultured astroglia prepared from rats or mice have been used to assess the metabolic properties of astroglia in vitro [3]. Basal glucose consumption by cultured rodent astroglia seems to be comparable to that by cultured rodent neurons. Interestingly, however, the amount of lactate that is released into the culture media is much higher in astroglial cultures than in neuronal cultures (Figure 5) [3, 23],

Figure 9.
Astrocyte-neuron lactate shuttle hypothesis (ANLSH) (adapted from [3]).

Figure 10.
Glutamate stimulates [14C]deoxyglucose phosphorylation through a Na+-dependent glutamate transporter in rat cultured astroglia (adapted from [18]).

suggesting the occurrence of active aerobic glycolysis in astroglia. Although the glucose consumption of astroglia seems to be comparable to that of neurons, the in vivo location of astroglia in the brain may make glucose uptake more suitable [30–32]. In contrast, neurons are not in direct contact with microvessels. Therefore, avid glucose uptake by cultured neurons may not reflect glucose metabolism in vivo. Of course, glucose supplied from the microvessels diffuses into the extracellular space and can be taken up by neurons via their glucose transporters (Glut 3) (Figure 9) [3, 17]. In addition to glucose, lactate generated by astroglia and released into the extracellular space can also be taken up by neurons via neuronal MCT2 (Figure 9) [3, 17]. When both glucose and lactate are available, cultured neurons metabolize lactate preferentially (Figures 6 and 7) [3, 23].

Values are mean $\pm$ SD of quadruplicate wells.
n.s., not significant, * $p < 0.05$, ** $p < 0.01$ versus control
(ANOVA followed by Dunnett's test for multiple comparison)

Figure 11.
Effects of L-glutamate on lactate release measured directly in culture medium for rat astroglia (adapted from [23]).

Neuronal activation causes glutamate release in the synaptic cleft. The maximal concentration of glutamate can reach 1 mM, which is toxic to neurons. To prevent glutamate toxicity, the end-feet of astroglia, which envelope the synapse (tripartite synapse) [32], remove glutamate via glutamate transporters together with the co-transportation of Na^+ based on an inwardly lower Na^+ -gradient across the membrane [3, 16, 33]. This inwardly lower ionic concentration gradient is maintained by Na^+, K^+ -ATPase; thus, ATP production requires glucose as an energy substrate. So far, cultured astroglia typically show high glucose utilization and lactate production, and these profiles are exaggerated by the addition of glutamate. Recently, we evaluated astroglia that had differentiated from human induced-pluripotent stem (iPS) cells and observed the conservation of similar metabolic profiles [54]. These results suggest that glutamate uptake enhances the consumption of glycolysis-derived ATP. Of note, glutamate in astroglia is converted into glutamine and recycled back to neurons (glutamate-glutamine cycle) (Figure 5) [3]. In addition, some of this glutamate is converted to α -ketoglutarate and utilized as a TCA cycle substrate (Figure 12) [3–5]. The capacity for glutamate oxidation is greater in astroglia than in neurons (Figure 13) [unpublished data]. Moreover, recent findings

Figure 12.
Glutamate taken up by Na⁺-dependent glutamate transporters enhances astroglial energy metabolism (both glycolytic and/or oxidative) (adapted from [3]).

Figure 13.
[1-¹⁴C]glutamate oxidation (CO₂ production from glutamate) in astroglia and neurons.

suggest that malate, an intermediate TCA metabolite, contributes to lactate production through its conversion into lactate via malic enzyme (**Figure 14**) [3].

5. Fates of lactate produced by astroglia

Whether lactate produced and released from astroglia can be used as an energy substrate by neurons has long been debated [36–53]. Theoretically, MCT4 in astroglia

Figure 14.
Glutamate taken up by Na^+ -dependent glutamate transporters enhances lactate production through a glycolytic pathway as well as through malic enzyme activation in astroglia (adapted from [3]).

Figure 15.
Increasing lactate concentrations (1–3 mM) enhance $[^{14}\text{C}]\text{lactate}$ oxidation in cultured neurons (adapted from [23]).

export lactate outside such cells, and MCT2 in neurons take up lactate [3, 17]. Once lactate enters a neuron, it could become a preferential energy substrate, compared with glucose; this pathway is known as the astrocyte-neuron lactate shuttle model (Figure 5) [3, 33]. In our in vitro culture model, increasing the concentrations of lactate enhanced the neuronal oxidation of lactate (Figure 15) [23]. The argument against this model is based on the high affinity of MCT2, which results in the rapid saturation of lactate transportation into neurons [52, 53]. Thus, astroglial lactate production does not favor neuronal lactate utilization. The validity of this model should be elucidated in vivo.

Lactate plays a role as a signal molecule. BDNF expression can also be induced by lactate through the activation of Sirtuin1 deacetylase. SIRT1 increases the levels of the transcriptional coactivator PGC-1 α and the secreted molecule FNDC5, known to mediate BDNF expression [13, 14]. Moreover, hydroxycarboxylic acid receptor 1 (HCAR1) has been found to act as a lactate receptor that results in the suppression of neuronal activity [55–57]. Lauritzen et al. showed that HCAR1 at the BBB was essential for mediating the effects of exercise on angiogenesis in a mouse model [56]. Furthermore, lactate binding to HCAR1 on neurons inhibits adenylate cyclase and thus decreases cAMP, thereby reducing neuronal activity and gene regulation. The potential negative modulation of BDNF production by lactate through HCAR1 should be examined more closely in the future.

6. Astroglia produce ketone bodies, which serve as neuronal energy substrates

In addition to BHB, acetoacetate and acetone are listed as ketone bodies. During starvation, ketone body production by hepatocytes in the liver is enhanced [3–5]. Astroglia in the brain function similar to hepatocytes and generate more ketone bodies than neurons (**Figure 16**) [3, 25]. The production of BHB is regulated by the AMP/ATP level, or the cellular energy state. AMP-activated protein kinase (AMPK) can sense a decrease in ATP and the resultant increase in AMP, which induces the activation of AMPK. Decreased malonyl-CoA stimulates the beta-oxidation of long-chain fatty acids, enhancing the production of acetoacetate and BHB. 5-Amino-1-b-D-ribofuranosyl-imidazole-4-carboxamide (AICAR), an activator of AMPK, stimulates these two ketone bodies in astroglia (**Figure 17**) [3, 25]. Similar to lactate, BHB is exported via MCT4 and is then imported into neurons through MCT2 and used as an alternative energy substrate [3, 17]. Unlike glucose-derived lactate, which needs to be converted to acetyl-CoA by PDHC to enter the TCA cycle, BHB enters the TCA cycle in an PDHC-independent manner. PDHC is susceptible to cellular stressors like reactive oxygen species (ROSs). Enhanced lactate production under brain ischemia triggers the accumulation of lactate. Unfortunately, however, re-perfusion therapy might not be helpful when PDHC is

Figure 16. [$1\text{-}^{14}\text{C}$]palmitic acid (PA) derived- CO_2 and acid-soluble fractions (ketone bodies: KBs) in rat neurons and astroglia (adapted from [25]).

Figure 17.
Ketogenesis by astroglia and neurons by 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), a cell-permeable activator of AMPK (500 μ M) (adapted from [25]).

Figure 18.
Effects of 1% hypoxia (24 h) on oxidative metabolism of lactate (LAC), pyruvate (PYR), or β -hydroxybutyrate (BHB) in neurons (adapted from [25]). Neuronal utilization (oxidative metabolism) of LAC and PYR was significantly reduced after hypoxia, while BHB oxidation was preserved.

damaged, since lactate is incapable of being utilized even in the presence of re-supplied oxygen (**Figure 18**). In contrast, neurons can utilize BHB instead of lactate, and ATP production can be restored after re-oxygenation (**Figure 18**) [3, 25].

7. BHB acts as an HDAC inhibitor and as a ligand of HCAR2

Vigorous physical exercise induces BHB production by the liver, but astroglial BHB production under similar conditions has not been confirmed.

Liver-derived BHB acts as a direct Class I HDAC inhibitor. By inhibiting HDAC2 and HDAC3 and preventing their recruitment to the BDNF promoter I, BHB induces BDNF expression [15, 16]. As described above, ischemic insults do, indeed, activate astroglial BHB production. Therefore, BHB-induced BDNF may help neuronal regeneration after ischemic damage. Further study is warranted. BHB released from astroglia also acts as a ligand of hydroxycarboxylic acid receptor 2 (HCAR2) and exerts neuroprotective effects by activating HCAR2, which in turn promotes the downstream activation of silent information regulator 1 (SIRT1) and inhibits nuclear factor-kappa B (NFκB) to protect against oxidative stress [58–61].

8. BHB can play a role in remyelination in the white matter of the brain

In terms of functional recovery, both the neuronal structure and myelination are essential [3, 7]. As for the energy supply, the white matter axons of neurons are myelinated by oligodendrocytes. The astroglial end-feet are in direct contact with neurons only at Ranvier nodes, implying that neither glucose nor lactate can reach neurons easily. In fact, axonal metabolic demand is fulfilled by lactate supplied by oligodendrocytes. How lactate is generated by oligodendrocytes remains to be elucidated. Since astroglial end-feet are suitable for the uptake of glucose from microvessels, lactate generated in astroglia could be transported to oligodendrocytes; alternatively, a pathway involving the direct uptake of glucose by oligodendrocytes could be involved. Importantly, myelin damage (demyelination) can occur in various neurological disorders, while the remyelinating capacity can potentially restore damaged myelin (remyelination). Myelin cholesterol synthesis is essential for such a process, and BHB could be a possible substrate [62–65]. Moreover, BDNF reportedly facilitates myelination [66].

9. Summary

Brain function is dependent on glucose, which is supplied from outside the brain as food. The unavailability of glucose forces the brain to utilize ketone bodies, especially BHB. In addition to glucose and BHB, lactate is another possible energy source for the brain. Physical exercise enhances the production of both lactate and BHB. The former is generated in skeletal muscles, while the latter is generated in liver hepatocytes. Interestingly, astroglia can generate both lactate and BHB inside the brain upon neuronal excitation. Astroglia-derived lactate and BHB can serve as alternative energy substrates, since physical activities are initiated by neuronal excitation, which cause astroglia to generate lactate and BHB inside the brain. Irrespective of the origins of lactate and BHB, both can be transported into neurons and simulate BDNF production, facilitating neurotransmission and synaptic plasticity. Thus, physical activity helps the human brain to function in a healthy manner through a metabolic compartment composed of glial cells, skeletal muscles, and liver.

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Disclosure

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Abbreviations

AICAR	5-amino-1-b-D-ribofuranosyl-imidazole-4-carboxamide
AMPK	AMP-activated protein kinase
BHB	beta-hydroxybutyrate
BBB	blood–brain barrier
BDNF	brain-derived neurotrophic factor
CBF	cerebral blood flow
CMR _{glc}	cerebral metabolic rate of glucose
CMR _{oxy}	cerebral metabolic rate of oxygen
FNDC5	fibronectin type III domain-containing protein 5
Glut1	glucose transporter 1
Glut3	glucose transporter 3
HDAC	histone deacetylase
HCAR1	ydroxycarboxylic acid receptor 1
HCAR2	hydroxycarboxylic acid receptor 2
iPS cell	induced-pluripotent stem cell
MCTs	monocarboxylate transporters
NFκB	nuclear factor-kappa B
PGC-1α	peroxisome proliferator-activated receptor gamma coactiva- tor 1-alpha
PDHC	pyruvate dehydrogenase complex
ROSs	reactive oxygen species
SIRT1	silent information regulator 1
TCA	tricarboxylic acid

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