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TABLE OF CONTENTS

VETERINARY SCIENCES

BIOLOGICAL SCIENCES

MEDICAL SCIENCES

ROLE OF KETONE BODIES IN NEUROTRANSMITTER (GABA, GLUTAMATE) METABOLISM DURING EXCESS NEURONAL ACTIVITY

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Introduction. Ketone bodies – β-hydroxybutyrate (BHB), acetoacetate (AcAc), and acetone – are not only alternative energy sources but also play a modulatory role in the regulation of neurotransmitter fluxes. Ketone metabolites are synthesized in the liver from fatty acids in response to reduced glucose availability, such as during fasting or adherence to a ketogenic diet. Under these conditions, they serve as alternative energy substrates for the peripheral tissues. After being transported into cells via monocarboxylate transporters (MCT1 and MCT2), ketone bodies are converted in the mitochondria of cells of peripheral organs and tissues, particularly for the brain, into acetyl-CoA, which enters the Krebs cycle and generates ATP. Thus, during a ketogenic diet, they provide stable energy supply and contribute to metabolic adaptation. In the brain, where the balance between glutamatergic and GABAergic activity determines the level of neuronal excitability, metabolic changes induced by ketone bodies are extremely important. The ketogenic diet, which induces excessive ketogenesis, has demonstrated high efficacy in the treatment of drug-resistant epilepsy and other neurological disorders. Research over the past decades has shown that ketone metabolites directly affect the cellular redox state, enzyme activity, and neurotransmitter synthesis pathways, making them key modulators of neuronal activity.

Aim. The aim of this study is to investigate the role of ketone bodies in regulating GABA and glutamate metabolism, analyze their inhibitory effects on neuronal excitability, and evaluate the metabolic mechanisms underlying the anticonvulsant action of the ketogenic diet.

Materials and Methods. This study analyzed current data from neurobiological, neurometabolic, biochemical, and clinical research. A comprehensive review of in vitro and in vivo experimental results was conducted, focusing on ketone body oxidation in neurons and astrocytes, changes in redox balance, regulation of tricarboxylic acid (TCA) cycle enzyme activity, and amino acid metabolism. Clinical observations on the efficacy of the ketogenic diet in patients with increased neuronal activity and epileptic seizures were also considered.

Results and Discussion. During ketogenesis, GABA utilization is partially impaired due to competition for succinyl-CoA, a key mitochondrial metabolite linking the Krebs cycle, GABA catabolism, and ketone body metabolism. Normally, GABA is metabolized via the GABA shunt, in which GABA transaminase converts GABA to succinic semialdehyde, and succinic semialdehyde dehydrogenase oxidizes it to succinate. Succinate is then converted to succinyl-CoA and enters the Krebs cycle.

However, during elevated ketone body formation, β-oxidation of fatty acids generates acetoacetate, which is converted into acetoacetyl-CoA by succinyl-CoA:-ketoacid CoA transferase (SCOT/OXCT1), consuming succinyl-CoA in the process. This reduces the availability of succinyl-CoA for the GABA shunt, slowing the conversion of succinate to succinyl-CoA and thus impairing GABA catabolism. As a result, intracellular GABA levels increase.

Glutamate, the principal excitatory neurotransmitter in the brain, is also tightly linked to GABA metabolism, as it serves as the direct precursor for GABA synthesis via glutamate decarboxylase (GAD). During ketogenic conditions, the partial impairment of GABA catabolism due to limited succinyl-CoA availability affects the glutamate-GABA balance. Ketone bodies, particularly BHB, can alter the utilization of glutamate in the Krebs cycle, allowing more glutamate to be converted into GABA. This metabolic shift contributes to an increased inhibitory tone in neuronal networks, complementing the anticonvulsant and neuroprotective effects observed under ketogenic dietary conditions.

Ketone bodies influence the glutamate–GABA balance by altering anaplerotic

and cataplerotic fluxes in neuronal metabolism. Elevated acetyl-CoA levels promote citrate synthesis, temporarily reducing the oxaloacetate pool needed for transamination reactions and favoring the conversion of glutamate into GABA. Simultaneously BHB oxidation generates NADH, which serves as a cofactor for the reductive amination of α-ketoglutarate catalyzed by glutamate dehydrogenase, producing additional glutamate available for GABA synthesis. Glutamate is then decarboxylated by GAD to form GABA, the primary inhibitory neurotransmitter. Together, these mechanisms enhance GABA production and strengthen inhibitory neurotransmission.

Astrocytes play a key role in maintaining neurotransmitter homeostasis by converting glutamate into glutamine, which is then supplied to neurons for GABA synthesis. Astrocytes actively take up glucose and, due to the predominance of glycolysis over oxidative metabolism, convert pyruvate into lactate via the LDH-A isoform of lactate dehydrogenase. The lactate produced is exported to neurons through the MCT1/MCT4 transporters to fuel their oxidative phosphorylation, forming the basis of the astrocyte–neuron lactate shuttle (ANLS). Because this shuttle relies on high astrocytic glycolytic flux, ketone body uptake by astrocytes reduces glucose consumption, suppresses glycolysis, and decreases pyruvate and lactate production, thereby enhancing oxidative phosphorylation and stabilizing the membrane potential. Additionally, ketone bodies modulate the metabolic flux between neurons and astrocytes: in neurons, increased acetyl-CoA and NADH enhance GABA synthesis and optimize the TCA cycle, while in astrocytes, ketones provide cataplerotic efflux of TCA intermediates for glutamine synthesis, supplying neurons with substrates for GABA production.

Enzymes catalyzing transamination and decarboxylation reactions, such as aspartate aminotransferase, GDH, and GAD, are highly sensitive to substrate levels and redox state. This allows cells to flexibly regulate the GABA/glutamate ratio depending on metabolic conditions, maintaining a balance between excitatory and inhibitory signaling.

Thus, ketone bodies not only meet the energy demands of neurons and

astrocytes but also play an important regulatory role in neurotransmitter metabolism, stabilizing neuronal activity and reducing the risk of hyperexcitability. These mechanisms explain the effectiveness of the ketogenic diet in conditions associated with excessive neuronal activity, including drug-resistant epilepsy.

Conclusions. Ketone bodies are critical modulators of neurometabolic processes and play a central role in maintaining the balance between inhibitory and excitatory neurotransmission. Their effects on redox state, enzymatic fluxes, and energy metabolism produce a powerful anticonvulsant effect, which underlies the clinical efficacy of the ketogenic diet. Understanding these mechanisms opens prospects for the development of new therapeutic approaches aimed at correcting metabolic disturbances in neurological disorders associated with hyperexcitability.