METABOLISM CLINICAL AND EXPERIMENTAL 81 (2018) XXX–XXX

Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Review

Metabolic strategies for the degradation of the neuromodulator agmatine in mammals

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ARTICLE INFO

Article history:
Received 1 March 2017
Accepted 8 November 2017

Keywords:
Mammals
Agmatine
Agmatinase

ABSTRACT

Agmatine (1-amino-4-guanidinobutane), a precursor for polyamine biosynthesis, has been identified as an important neuromodulator with anticonvulsant, antineurotoxic and antidepressant actions in the brain. In this context it has emerged as an important mediator of addiction/satiety pathways associated with alcohol misuse. Consequently, the regulation of the activity of key enzymes in agmatine metabolism is an attractive strategy to combat alcoholism and related addiction disorders.

Agmatine results from the decarboxylation of L-arginine in a reaction catalyzed by arginine decarboxylase (ADC), and can be converted to either guanidine butyraldehyde by diamine oxidase (DAO) or putrescine and urea by the enzyme agmatinase (AGM) or the more recently identified AGM-like protein (ALP). In rat brain, agmatine, AGM and ALP are predominantly localised in areas associated with roles in appetitive and craving (drug-reinstatement) behaviors. Thus, inhibitors of AGM or ALP are promising agents for the treatment of addictions. In this review, the properties of DAO, AGM and ALP are discussed with a view to their role in the agmatine metabolism in mammals.

Contents

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https://doi.org/10.1016/j.metabol.2017.11.005
0026-0495/

1. Introduction

Agmatine (1-amino-4-guanidinobutane) is a primary amine that is generated from the decarboxylation of L-arginine by arginine decarboxylase (ADC; EC 4.1.1.19: Fig. 1). In mammals, agmatine has been directly associated with many important cellular functions, including the modulation of insulin release from pancreatic cells [1–3], renal sodium excretion [4,5] and neuroprotective effects [6–9]; furthermore, agmatine inhibits all known isoforms of nitric oxide synthase (NOS) in the brain [10] and increases the tolerance to morphine [11]. Agmatine also plays an essential role in the regulation of the expression of ornithine decarboxylase (ODC) [12] (Fig. 1) and spermidine/spermine acetyl transferase [13], two enzymes that are involved in polyamine biosynthesis [14]. In the central nervous system (CNS), agmatine is considered to be a neurotransmitter/neuromodulator, because it is synthesized in the brain, stored in synaptic vesicles, accumulated by uptake and released by depolarization [15,16]. In addition, agmatine activates several membrane receptors, including

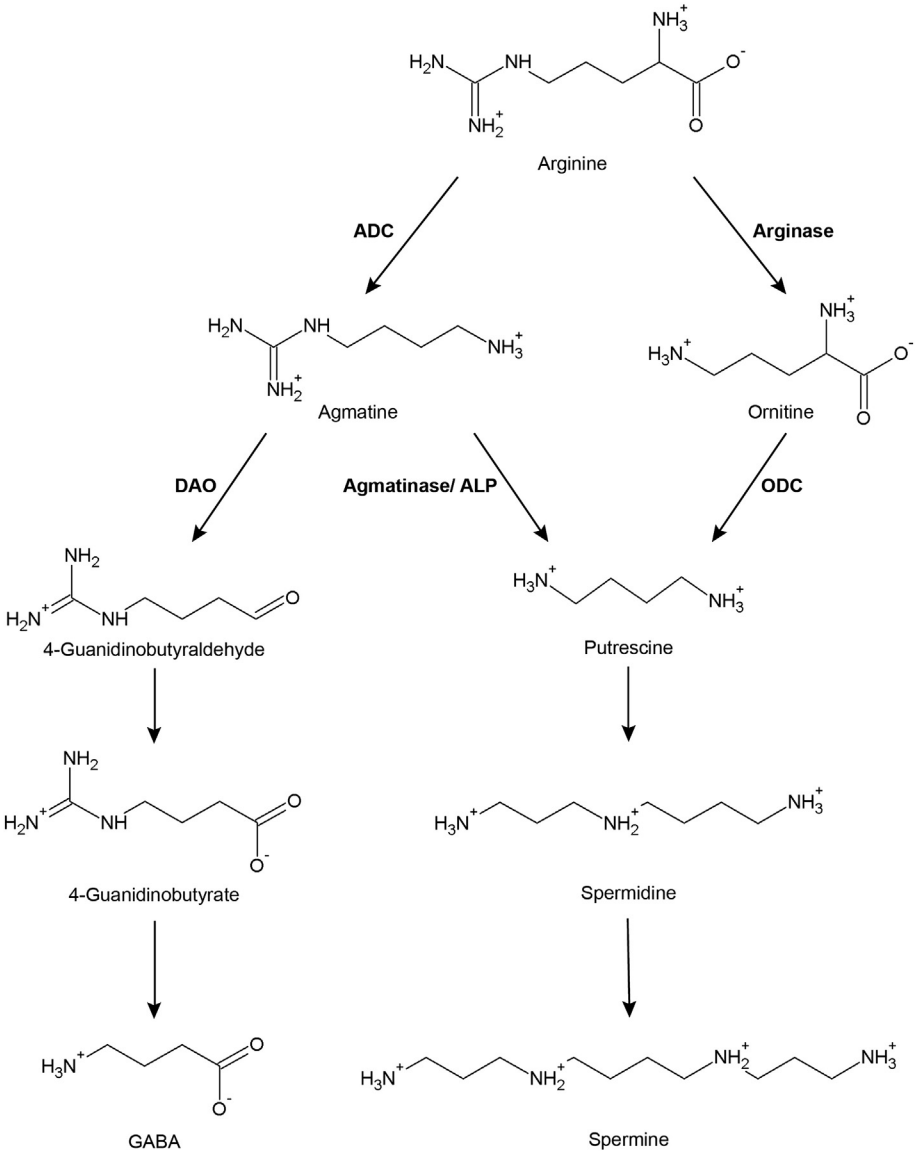

Fig. 1 – Metabolic pathways for agmatine synthesis and conversion to polyamines or GABA. Agmatine, produced from L-arginine by ADC, may be hydrolyzed to putrescine, either by AGM or ALP in the polyamine biosynthetic pathway, or converted to guanidinobutyraldehyde by DAO, for the synthesis of GABA. ODC decarboxylates arginine and is also capable to produce putrescine.

Please cite this article as: Benítez J, et al, Metabolic strategies for the degradation of the neuromodulator agmatine in mammals, Metabolism (2018), https://doi.org/10.1016/j.metabol.2017.11.005