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Metabolism and function in animal tissues of agmatine, a biogenic amine formed from arginine

Review Article

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Summary. Recently agmatine, decarboxylated arginine, has been shown to be an important biological compound in several animal tissues. This paper summarizes the known information regarding the transport of arginine, its decarboxylation and the effects of the agmatine formed mainly on NO and polyamine synthesis.

Keywords: Arginine – Agmatine – Arginine decarboxylase – Nitric oxide – Polyamines

Introduction

Arginine is the source of ornithine (and hence polyamines), nitric oxide (NO), creatine, glutamate and proline. It is also used for the biosynthesis of agmatine, an amine long known to be present in bacteria and plants, and now detected at very low concentrations in all animal tissues studied so far. Since it binds to the imidazoline receptors, most studies have been performed on the nervous system and it is thought to act as a central neurotransmitter, though other effects have been demonstrated. The metabolism and function of agmatine in the nervous system have formed the subject of a recent review (Reis et al., 2000). This paper is mainly concerned with its other functions.

Agmatine distribution in tissues

Agmatine is widely and unevenly distributed in mammalian tissues. Observed first in the rat brain, it was shown later that in the rat the concentration in this organ (2.40 ng/g) is lower than in others, such as stomach (71.00 ng/g), intestine, spleen and liver (5.63 ng/g), though variations between strains and between animals of the same strain have also been recorded (Raasch et al., 1995). More recently higher values were reported for the intracellular concentration of agmatine in some rat tissues (Lortie et al., 2000).

It is also detectable in human plasma and higher concentrations have been observed in depressed patients (Halaris et al., 1999).

Biosynthesis

Agmatine is formed by decarboxylation of arginine catalysed by mitochondrial arginine decarboxylase (ADC) (Li et al., 1995). Arginine itself is a semi-essential amino acid synthesised by most cells. Its uptake is important and its main transport mechanism is system y^+, a high-affinity, Na^+-independent transporter of basic amino acids. Four genes (*CAT-1*, *CAT-2*, *CAT-3* and *CAT-4*) encode these transporters. *CAT-1* is ubiquitous (apart from the liver), whereas expression of the other three is more restricted. Differential splicing of the CAT-2 mRNA gives rise to two CAT-2 isoforms: CAT-2A, a low-affinity transporter insensitive to trans-stimulation and mainly expressed in the liver (Kavanaugh et al., 1994) and CAT-2B, a high-affinity transporter characterised by trans-stimulation. Expression of the poorly efficient CAT-2A in the liver may prevent the entry of arginine and its hydrolysis by arginase I.

The extent to which arginine is transported into mitochondria and the mechanism involved are not clear. In rat brain mitochondria, it is taken up by both a high and a very low affinity component, probably due to diffusion.

This uptake is prevented by basic amino acids, resembling the y^+ system operating in some nervous cells, though different in some respects from the non-mitochondrial system (Dolinska et al., 1998). In the liver, arginine enters mitochondria by exchange with citrulline (Indiveri et al., 1992). Moreover we have shown that it is taken up by an energy-independent mechanism. This is sensitive to arginine and probably reflects membrane binding rather than transport into the matrix (Salvi et al., in press). In this way arginine is exposed to ADC as well as to arginase II and to the mitochondrial NO synthase (NOS) (Giulivi et al., 1998).

Arginine decarboxylation, originally ascribed to ornithine decarboxylase (ODC) (Gilad et al., 1996), is now known to occur by effect of the specific enzyme ADC. By contrast with ODC, ADC is labile, rapidly inactivated at room temperature, located in the mitochondria and not in the soluble part of the cells, not affected by difluoromethylornithine (DFMO), and inhibited by Ca^{++}, Co^{++} and polyamines. The two enzymes also differ in their organ distribution and regulation (Regunathan et al., 2000).

The mutual regulation of the arginine pathways in mitochondria is not well known. The reciprocal regulation of arginase and NOS has been studied in some cell types. In murine macrophages, for example, Th1 cytokines induce NO synthesis and suppress arginase, whereas Th2 cytokines induce arginase and suppress NO synthesis. The NO synthesis/arginase balance is also regulated in this way in murine dendritic cells (Munder et al., 1999). Moreover, N^G-hydroxy-L-arginine (NOHA), the intermediate of NO synthesis, if released during the reaction, inhibits arginase (Daghigh et al., 1994; Boucher et al., 1994). It follows that when NOHA concentration is increased, as it occurs in serum of LPS treated rats (Hecker et al., 1995), arginase activity can be inhibited, as least in aortic endothelial cells. This mechanism may ensure sufficient arginine for a high NO output (Buga et al., 1996). In addition, extracellular arginine increases NO production, though its intracellular concentration is such as to saturate the enzyme. Several explanations of this ‘‘Arginine paradox’’ have been advanced. It has been suggested, for example, that in intact cells NOS isoforms are inhibited *in vivo* and *in vitro* by endogenously produced compounds, such as N^G,N^G-dimethylarginine (asymmetric dimethylarginine: ADMA) and N^G-methylarginine (NMA). Arginine administration would thus enhance the concentration of intracellular arginine and promote an exchange of intracellular inhibitors with extracellular arginine in NOS-producing cells (Tsikas et al., 2000). This effect would depend on the amount of arginine administered and last as long as the circulating arginine concentration was higher than the pre-administration concentration.

Investigation of the interrelation between arginase and NOS in macrophages has revealed stimulation of the arginase pathway and inhibition of the iNOS pathway during tumor growth. It was shown that intratumor macrophages shift arginine metabolism to ornithine or NO and that these shifts are strongly correlated with tumor growth and rejection respectively (Mills, 2001).

Little attention has so far been directed to the involvement of agmatine in this mutual regulation. It inhibits NOS, especially the inducible isoform (Galea et al., 1996), and may be an endogenous regulator of NO production even though it is a rather weak competitive inhibitor. Some of the biological effects it mediates may thus be due to interaction with the ubiquitous NO system. Other studies indicate that agmatine also causes a time-dependent, irreversible inactivation of nNOS at concentrations 10-fold lower than those observed for competitive inhibition, and a 3-fold increase in the NADPH oxidase activity of nNOS leading to formation of the H_2O_2 (Demady et al., 2001) that may be responsible for oxidative alteration of the heme prosthetic group.

Transport

Agmatine is both formed *in situ* and taken up by exogenous sources, as it is present in food and is produced by the intestinal flora (Raasch et al., 1995). The uptake occurs in a variety of cells through several mechanisms. In the nerve cells it is apparently transported by selective systems: in rat brain synaptosomes, this seems to be a cation channel that may be shared by Ca^{++} but not by other amines (Sastre et al., 1997); in SK-MG-1, a human glioma cell line, uptake is via another selective transporter (Molderings et al., 2001). The existence of these selective mechanisms is apparently related to agmatine's function as a neuromodulator/neurotransmitter (Reis et al., 1998).

In the other cells, transport is supposed to be mediated by the polyamine transport system, which is mostly formed of two different carriers, one Na^+-dependent and the other Na^+-independent and also at least partially energy dependent. This has been shown for the transport into rat hepatocytes (Cabella et al., 2001) and in some kidney cell lines (Satriano et al., 2001a). In most cases competition between the uptake of agmatine and that of putrescine has suggested that they use the same

transporter. Regulation of intracellular polyamines by agmatine has also been postulated. According to Satriano et al. (1998), this could take place via induction of the ODCantizyme, which suppresses both the polyamine biosynthetic enzyme ODC and polyamine transporters. Experiments with mouse kidney proximal tubule cells (MTC) have shown that this is the case, whereas in rat hepatocytes (Cabella et al., 2001) and pulmonary artery endothelial cells (Babal et al., 2001) a role for ODCantizyme in the effects of agmatine on polyamine transport was not confirmed. The dramatic increase of transport into DFMO-treated hepatocytes indicates that it depends on the intracellular polyamine pool (Cabella et al., 2001). According to Iyer et al. (2002), agmatine taken up would enable tumor cells to obtain polyamines even in the absence of the exogenous compounds and with low ODC activity.

Synaptosomes can both take up agmatine and release it by depolarisation in a Ca^{++}-dependent manner (Reis et al., 1998). This means that their agmatine content can be tightly regulated. Moreover the existence of discrete transporters in individual cell types may be of significance in the regulation of intracellular agmatine and polyamine distribution.

Metabolism

In plants, transformation of agmatine is seen as one of the main routes for polyamine synthesis via putrescine and N-carbamoylputrescine (Smith, 1984). The reactions involved in agmatine metabolism in mammals are summarised in Fig. 1. Agmatine is hydrolysed by agmatinase to putrescine and urea, or oxidised by diamine oxidase (DAO) to γ-guanidinobutyraldehyde, which is then oxidised to γ-guanidinobutyrate.

In hepatocyte cultures, only 10% of agmatine is transformed into polyamines (Cabella et al., 2001), probably by agmatinase. Recently human agmatinase has been cloned in two laboratories (Iyer et al., 2002; Mistry et al., 2002). Its mRNA is expressed in several tissues, particularly liver and kidneys. It remains to be determined whether the agmatinase RNA level corresponds to agmatinase activity. The significant similarity of the human enzyme to the bacterial enzymes makes it a member of the arginase superfamily. It probably requires two divalent manganese ions like the E. coli enzyme. Since agmatinase mRNA is markedly elevated in liver infected by hepatitis B virus, inhibition of the enzyme's activity or expression has been proposed as a new way of treating viral hepatitis (Mistry et al., 2002).

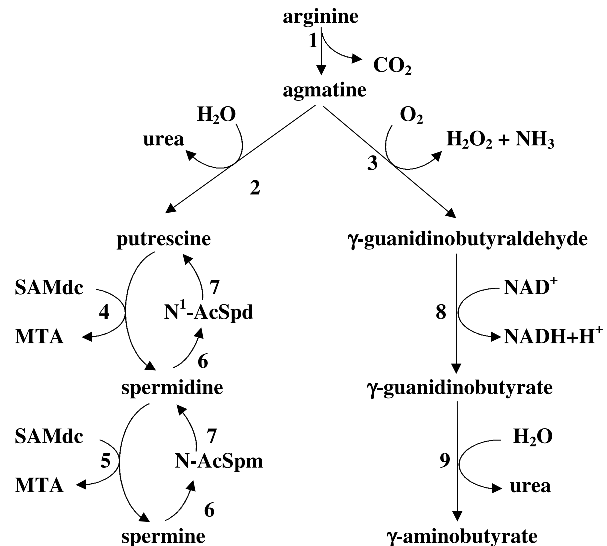

Fig. 1. Metabolism of agmatine. *1*, arginine decarboxylase; *2*, agmatinase; *3*, diamine oxidase; *4*, spermidine synthase; *5*, spermine synthase; *6*, spermidine/spermine acetyltransferase; *7*, polyamine oxydase; *8*, aldehyde dehydrogenase; *9*, hydrolase; *MTA*, methylthioadenosine; *N^1-AcSpd*, N^1-acetylspermidine; *N-AcSpm*, N-acetylspermine; *SAMdc*, decarboxylated S-adenosyl- methionine

In hepatocytes, about 50% of agmatine is transformed by DAO into γ-guanidinobutyraldehyde and then into γ-guanidinobutyrate. γ-Aminobutyrate (GABA) is also accumulated if a GABA transaminase inhibitor is present (Cabella et al., 2001). In rat kidney, agmatine is also a substrate for amino oxidases, whereas in the brain agmatinase appears to be responsible for agmatine metabolism (Reis et al., 2000). Agmatinase activity similar to that in brain has also been observed in macrophages (Sastre et al., 1998). It is increased by LPS, whereas ADC is reduced. This is thought to result in regulation of the concentration of agmatine and control of its effects on NOS and polyamine synthesis.

Functions

Agmatine initially attracted attention because it binds to the imidazoline receptors and stimulates the release of catecholamines from adrenal chromaffin cells (Li et al., 1994). It was then shown to modulate the function of N-methyl-D-aspartate (NMDA) receptor channels by selectively blocking the subclass of glutamate receptor channels (Yang et al., 1999). This blockade is mediated by interaction between the guanidine group and the pore of the NMDA receptor channel. This observation is interesting, since agmatine enhances opioid analgesia and prevents *in vivo* tolerance (Kolesnikov, 1996). In rodents,

agmatine decreases hyperalgesia accompanying inflammation, neuropathy and spinal cord injury (Fairbanks et al., 2000). These actions may be mediated by antagonism with the NMDA receptors and/or, as we shall see, NOS inhibition. Since agmatine is present in the spinal cord, the endogenous compound may have the same role. All these results corroborate the view that agmatine is an endogenous neuromodulator/neurotransmitter, as suggested by the initial findings.

It has since been demonstrated that agmatine has an effect on polyamine metabolism and NOS activity, and is also involved in apoptosis and/or necrosis.

The effect of agmatine on cell polyamine content has been studied in hepatocytes. When cultured in the presence of agmatine, their spermidine and spermine content decreases, whereas putrescine is increased and N^1-acetylspermdine becomes detectable. This effect is already evident with 0.01 mM agmatine and is proportional to its concentration. These changes are due to an increase in spermidine/spermine acetyltransferase (SSAT) activity and SSAT protein content. ODC activity is slightly reduced, whereas S-adenosylmethionine decarboxylase is significantly increased (Vargiu et al., 1999).

Agmatine has been postulated as a promoter of apoptosis since this is correlated with a decrease in polyamines. Culture of hepatocytes in the presence of agmatine results in a marked increase in the number of apoptotic cells accompanied by mitochondrial swelling, release of cytochrome c and increased caspase-3 activity. These changes are interpreted as a consequence of oxidation of agmatine by DAO followed by H_2O_2 synthesis (Gardini et al., 2001). A different effect was observed when agmatine was investigated on proliferating cells, namely HTC cells. Here, too, there was a dramatic polyamine depletion due to reduced ODC activity and expression, and higher SSAT activity, but no apoptosis, though the cytoskeleton was altered and proliferation was inhibited: these two effects were reversed when spermidine was added. It would thus seem that the intracellular polyamine pool is the main target of the polyamine cytostatic effect and that polyamines themselves are of importance in the organisation and stabilisation of the cytoskeleton (Gardini et al., 2002). In H-ras transformed NIH/373 cells, agmatine's antiproliferative effect is also independent of apoptotic attrition. Instead, reversion from a transformed to a senescent phenotype is observed (Satriano, 2002).

As mentioned earlier, agmatine is a competitive inhibitor of NOS, particularly its inducible isoform (Galea et al., 1996). According to Satriano et al. (2001b), it is

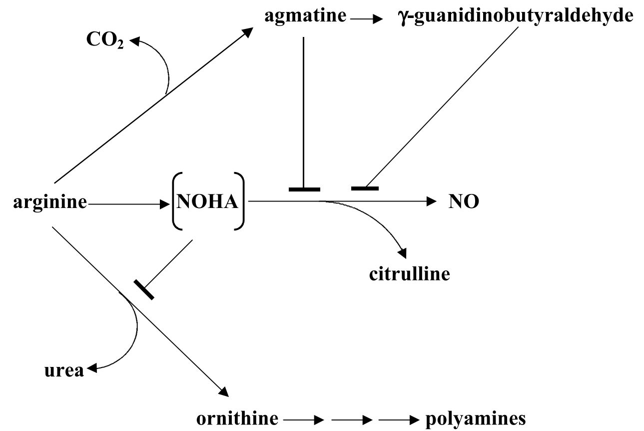

Fig. 2. Interregulation of the pathways leeding to agmatine, NO and polyamines

the γ-guanidinobutyraldehyde responsible for inhibition of NO synthesis by iNOS. The pathways are closely interregulated: high NO levels suppress aldehyde dehydrogenase (AldDH) activity; induction of DAO expression and activity (Sessa et al., 1990) lead to the formation of γ-guanidinobutyraldehyde. This inhibits NO synthesis and arginine is spared for polyamine synthesis to support growth. As NO decreases, AldDH increases and γ-guanidinobutyraldehyde will be transformed into γ-guanidinobutyrate. Agmatine may thus be supposed to help in coordinating NO regulation and polyamine synthesis (Fig. 2).

Whatever the mechanism, inhibition of NOS gives rise to several effects owing to NO's many functions. Since, for example, NO inhibits ODC by nitrosylating 4 cysteine residues, including Cys 360, a critical thiol residue in its active site (Bauer et al., 2001), ODC activity and cellular polyamine uptake may be negatively regulated without the involvement of antizyme (Satriano et al., 1999) in addition to the antizyme mechanism (Satriano et al., 1998).

The effect *in vivo*, however, may be different. Agmatine, in fact, increases or decreases the expression of NOS in function of cell type. In endothelial cells it increases NO synthesis. This suggests that agmatine binds to a cell surface imidazoline receptor and stimulates NO production by increasing cytosolic calcium (Morrissey et al., 1997). In microglia, on the other hand, agmatine suppresses LPS-induced NO production (Abe et al., 2000). In rats with Thy-1 nephritis, agmatine also decreases NO production and cell proliferation (Ishizuka et al., 2000), and thus improves the nephron filtration rate and renal function.

Concluding remarks

It is clear, therefore, that agmatine is also an important arginine metabolite in mammals. In addition to binding to some receptors in the nervous system and modulating their activity, it promotes actions in many other tissues. The pathways of arginine metabolism appear to be interregulated. Agmatine metabolism may thus act as a switch between polyamine and NO synthesis and agmatine itself may be involved in proliferation, apoptosis, inflammation and other processes.

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