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Review

Amino acids – A life between metabolism and signaling

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ABSTRACT

Amino acids serve as constituents of proteins, precursors for anabolism, and, in some cases, as signaling molecules in mammalians and plants. This review is focused on new insights, or speculations, on signaling functions of serine, γ-aminobutyric acid (GABA) and phenylalanine-derived phenylpropanoids. Serine acts as signal in brain tissue and mammalian cancer cells. In plants, *de novo* serine biosynthesis is also highly active in fast growing tissues such as meristems, suggesting a similar role of serine as in mammalians. GABA functions as inhibitory neurotransmitter in the brain. In plants, GABA is also abundant and seems to be involved in sexual reproduction, cell elongation, patterning and cell identity. The aromatic amino acids phenylalanine, tyrosine, and tryptophan are precursors for the production of secondary plant products. Besides their pharmaceutical value, lignans, neolignans and hydroxycinnamic acid amides (HCAA) deriving from phenylpropanoid metabolism and, in the case of HCAA, also from arginine have been shown to fulfill signaling functions or are involved in the response to biotic and abiotic stress. Although some basics on phenylpropanoid-derived signaling have been described, little is known on recognition- or signal transduction mechanisms. In general, mutant- and transgenic approaches will be helpful to elucidate the mechanistic basis of metabolite signaling.

Contents

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1. Introduction

All life depends on a constant flow of metabolites that provide building blocks as well as energy and reducing power for growth, development, and reproduction. Beside of their role in biochemistry, metabolic intermediates can also serve as signaling molecules contributing to the complex regulatory network that eventually adapts gene expression to altered requirements during the life cycle, or as a response to a changing environment. In this review we focus on the dual functions of certain amino acids and their derivatives as metabolic intermediates/end-products and signaling molecules. Such dual functions are well documented in the medical/mammalian field, and evidence for similar functions is also emerging for the plant system.

The amino acid serine has recently been suggested to act as a signal controlling the proliferation of mammalian cancer cells [1,2]. As the demand for nutrients in fast growing cells is high, the nutritional state determines the rate of cell proliferation. In plants, *de novo* serine biosynthesis is highly active in fast growing tissues, such as meristems [3] suggesting a similar role of serine as signaling molecule in plants.

Likewise, in the mammalian brain glutamate-derived γ-amino butyric acid (GABA) is an inhibitory neurotransmitter that exerts its signaling effect after binding to specific receptors [4]. In plants, evidence for GABA-dependent signal transduction pathways exists and awaits a detailed characterization.

Besides their role as constituents of proteins, the aromatic amino acids phenylalanine, tyrosine and tryptophan are the precursors for a variety of secondary products [5,6] among them compounds with signaling function. The phenylpropanoid pathway, starting from phenylalanine delivers, for instance, the neolignan dehydrodiconiferyl alcohol glucoside (DCG), which has been shown to exert cytokinine-like effects in plants [7–9]. Likewise, amines and polyamines deriving from the amino acid arginine together with the phenylpropanoid *p*-coumaric acid converge in the synthesis of hydroxycinnamic acid amides (HCAAs). HCAAs are involved in stress- and pathogen responses and might also act as signaling molecules during developmental processes [10].

Fig. 1 shows an overview on the compartmentation of anabolic and catabolic pathways in a mesophyll cell including branch points leading to those metabolic signals that are highlighted in this review. In contrast to catabolism, which is mainly localized in the cytosol or mitochondria, the majority of the anabolic reaction sequences are initiated in the plastid stroma. Chloroplasts are the site of CO_2-, ammonia- and sulphur assimilation and of a variety of pathways leading to the biosynthesis of building blocks like fatty acids [11], aromatic amino acids [5,6], branched chain amino acids [12], isoprenoids *via* the mevalonate-independent way (methylerythritol 4-phosphate pathway; [13], serine [3,14], and arginine [15]). The glycolytic intermediate phosphoenolpyruvate (PEP) obviously plays a central role both in anabolism and catabolism [16] and hence also in the production of amino acid derived signaling molecules.

In this review we elucidate the dual or multiple functions of serine, GABA, neolignans like DCG as well HCAAs with respect to metabolism and signaling. Mutant plants impaired in the biosynthesis of amino acids or downstream products might help to dissect the involvement of amino acid metabolism in cellular signaling processes.

2. Serine, a key regulator for development?

2.1. Serine, an indispensable metabolite

In addition to its role as constituent of proteins, L-serine is a precursor for the biosynthesis of a multitude of metabolites. For instance, it is required for the biosynthesis of the amino acids glycine, cysteine and tryptophan (for the latter see Fig. 1), or for the biosynthesis of lipids like sphingolipids and phosphatidylserine [17,18]. In addition L-serine delivers one-carbon units for the tetrahydrofolate metabolism [19]. In most organisms L-serine is synthesized by the glycolytic or 'phosphorylated' pathway, in which 3-phosphoglycerate is converted to phosphoserine and subsequently to L-serine [3]. However, in plants, L-serine is predominantly generated during the overall process of photorespiration [14]. As photorespiration is tightly coupled to photosynthesis, this path of L-serine production is restricted to autotrophic tissues. In addition to photorespiratory L-serine biosynthesis, plants contain all genes essential for the 'phosphorylated' pathway [3,20]. These genes are highly expressed in non-photosynthetic tissues like roots or in the regions of primary meristems, where cell proliferation takes place. Mutant plants deficient in the 'phosphorylated' pathway are embryo lethal, underlining the importance of this path of L-serine biosynthesis. Moreover, even if the activity of this pathway was only diminished by artificial silencing of genes involved, it resulted in severely impaired leaf and root development [3,20]. However, these developmental constraints cannot be explained by a general decrease in L-serine contents, because these remain unaltered in transgenic plants [3,20]. At the present state it has not been resolved yet whether the observed developmental constraints are simply based on metabolic limitations or whether L-serine functions as a growth-regulating signal itself as it has been reported for other organisms.

2.2. Serine, a metabolic signal?

Recently it has been shown that D-serine, synthesized by serine racemase from proteinogenic L-serine, occurs in plants. D-Serine functions as a signaling molecule in the communication between male gametophytes and the pistil by regulating a glutamate receptor-like Ca^{2+} channel in the apical region of pollen tubes [21]. This regulatory mechanism resembles those known from mammalians, where D-serine functions as neurotransmitter in the brain and regulates the activity of the N-methyl-D-aspartate receptor, a non-selective ion channel [22]. In plants, not only D-serine, but also L-serine is supposed to act as metabolic signal. Deletion of the gene encoding the photorespiratory enzyme hydroxypyruvate reductase1 only affected the L-serine content in the respective mutants, but not the contents of most metabolites. Moreover, the mutation in this gene leads to a considerable change in expression of photorespiration-related genes. Similar alterations in gene expression pattern have been observed for wild-type plants grown on a medium supplemented with physiological concentrations of L-serine [23]. Nevertheless, it remains elusive whether or not L-serine is directly or indirectly responsible for the deregulation of photorespiratory genes.

Recently notable advances have been made on the path to understand the regulatory function of L-serine in mammalian cancer cells [24]. L-Serine plays an important role in controlling cell proliferation during cancer progression. On the one hand, the flux of 3-phosphoglycerate to L-serine synthesis *via* glycolysis is enhanced, to provide sufficient L-serine required for protein synthesis in the cancer cells, and on the other hand, also as carbon donor for one-carbon (C_1) metabolism. C_1-metabolism is the source for a large number of molecules essential for regeneration and proliferation of cells, such as S-adenosylmethionine, an important methyl-group donor, and purine bases required for DNA and RNA synthesis [1]. In proliferating cancer cells, L-serine controls the flux into C_1 metabolism by balancing the carbon flow between glycolysis and its own biosynthesis. Beside its signaling potential, L-serine functions as an allosteric activator of pyruvate kinase M2, an isoenzyme specific for embryo and tumor cells. In these cells

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