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THE RATIONALE FOR THE LOCALIZATION OF POLYAMINE PATHWAY ENZYMES IN THE BRAIN

BEYİNDEKİ POLİAMİN YOLAK ENZİMLERİNİN LOKALİZASYONUNUN ANLAMI

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Abstract

Polyamines, including spermidine, spermine, and agmatine, serve several brain-specific functions. Polyamine transport mechanisms may account for the redistribution of these organic cations, which may also be synaptically released as neuromodulators or neurotransmitters, in the brain. Therefore, the localization of polyamine pathway enzymes, in addition to the localization and functional investigation of the polyamines itself, provides valuable insights regarding the identification of cell- and region-specific roles for polyamines, notably in the context of mental disorders and neurodegenerative diseases. Identified neuronal circuits are subject to physiological and pharmacological investigations. With this respect, we electrophysiologically studied the cerebellar cortex and the medial habenula, showing a prominent synaptic expression of spermidine synthase and agmatinase, respectively. In both areas, the relevant polyamines clearly influence the electrical activity. The medial habenula may be involved with the aetiology of major depressive disorder. In this context, the expression of agmatinase in other brain areas, e.g. the paraventricular thalamic nucleus, possibly also involved with depression, is discussed.

Keywords: Polyamines, brain, neurobiology

Özet

Spermidin, spermin ve agmatini içeren poliaminler beyne özgü pek çok fonksiyonu çalıştırmaktadır. Poliamin dolaşım mekanizmaları, beyinde nöromodülatör ve nörotransmitterler gibi sinaptik olarak salgılanabilen bu organik katyonların yeniden dağıtımından sorumlu olabilmektedir. Bu nedenle, poliaminlerin lokalizasyon ve fonksiyon incelemesine ek olarak poliamin yolak enzimlerinin lokalizasyonu, özellikle psikolojik bozukluklar ve nörolojik dejeneratif hastalıklarda poliaminlerin hücre tanımlaması ve bölgeye özgü rolleriyle alakalı hatırı sayılır bilgiler sağlamaktadır. Belirli nöronal devreler fizyolojik ve farmakolojik araştırmalara bağlıdır. Bu çalışma kapsamında spermedin sentezi ve agmatinin belirli sinaptik ifadesini nispeten gösteren serebral korteksi ve medial habenulayı elektrofizyolojik olarak incelenmiştir. Her iki alanda da ilgili poliaminler açık bir şekilde elektriksel aktiviteyi etkilemekte ve medial habenula majör depresif rahatsızlığın etiyolojisinde yer alabilmektedir. Bu bağlamda, paraventriküler talamik nükleusu gibi beynin diğer bölümlerindeki agmatinin ifadesiyle depresyon ilişkisinin olasılığı tartışılacaktır.

Anahtar Kelimeler: *Poliamin, beyin, nörobiyoloji*

The naturally occurring polyamines putrescine, spermidine, and spermine and the guanidino-group-containing diamine agmatine, here together referred to as polyamines in the wider sense, represent evolutionary ancient biomolecules that are found throughout procaryotic and eukaryotic life forms, ranging from bacteria to animals and plants. Initially discovered as spermine cristals in human seminal fluid by Antoni van Leeuwenhoek in 1678 and subsequently further characterized between 1878 and 1926, by now polyamines have gained considerable interest as multifunctional cations. Given their multiple positive charges at physiological pH values, polyamines necessarily interact with negatively charged biomolecules, notably nucleic acids. Thus, the primary function of spermidine and spermine, containing three respectively four amino and imino groups, may be involved with the stabilization of RNA (Igarashi and Kashiwagi, 2000) and the tertiary structure formation of DNA and the condensation of chromatin (D'Agostino and Di Luccia, 2002; D'Agostino et al., 2006). Accordingly, polyamine synthesis and degradation is induced during progression of the cell cycle (Wallace et al., 2003). Polyamines are therefore essential for growth and differentiation of tissues. In contrast to relatively low polyamine concentrations in normally dividing cells that inhibit normal growth and proliferation control, cancer cells contain high amounts of polyamines while having lost growth and proliferation control (Gerner and Meyskens, 2004). Consequently, polyamine

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biosynthetic enzymes, notably ornithine decarboxylase (ODC), became therapeutic targets in cancer research (recently reviewed in (Nowotarski et al., 2013)). Being tightly controlled under normal conditions by multiple mechanisms, polyamine concentrations in most non-dividing cells can be expected to be rather low and mostly bound to other biomolecules. Therefore, in the adult brain, given a very limited potential for neurogenesis in restricted brain regions, one could assume that in most areas polyamine content and especially the expression of polyamine pathway enzymes could be marginable and may even be below detection limits. However, in contrast to putrescine, the polyamines spermidine and spermine were biochemically detected in relatively high amounts in brain (1995; Saka et al., 2002; Shaw, 1979; Shaw and Pateman, 1973), thus suggesting a specific role for polyamines in the central nervous system. Basically, four main lines of evidence subsequently supported this assumption: (1) the discovery of several prominent molecular targets for polyamines in the brain, beginning with NMDA receptors (Ransom and Stec, 1988), (2) the existence of polyamine transport systems in neurons, glial cells and synaptic vesicles (Masuko et al., 2003), (3) polyamine-dependent behavioural effects (Gupta et al., 2012; Liu et al., 2008a; Liu et al., 2008b; Seo et al., 2011), and the involvement with the pathophysiology of psychiatric disorders (reviewed in (Fiori and Turecki, 2008)), neurodegenerative diseases (Antony et al., 2003; Colton et al., 2004; Goers et al., 2003), and brain injury (Kim et al., 2009; Moretti et al., 2014). In addition to spermidine/spermine, also agmatine became increasingly important in this context (reviewed in (Uzbay, 2012)), after being discovered as an endogenous ligand of imidazoline receptors (Li et al., 1994) and discussed as a putative neurotransmitter (Reis and Regunathan, 1998a, b). The involvement of polyamines with mental disorders, namely schizophrenia and depression, came into focus, as side effects of the anti-malarial drug chloroquine, possessing a polyamine-like moiety, were observed in some patients (Andrews, 1985). Notably, in depressed patients, altered agmatine plasma levels were observed (Halaris et al., 1999), and in suicidal individuals the gene expression of the spermidine/spermine catabolic enzyme SSAT was found to be down regulated (Fiori et al., 2011). Moreover, in animal models of depression agmatine produced anti-depressant-like effects (Zomkowski et al., 2002). In addition, the polyamine system is involved with stress response (Gilad and Gilad, 2002, 2003). Thus, acute and chronic stress alter polyamine levels and ODC activity in the central nervous system. Consequently, the polyamine system is apparently involved with a key feature of depression, as it is known that, at least in a subset of phenotypes of depressive illness, the hypothalamo-pituitary-adrenal axis is over-activated with enhanced secretion of corticotropin releasing hormone (Antonijevic, 2008; Holsboer, 1988). Furthermore, another key feature in depression is the lack of getting any type of reward in these patients. Accordingly, an involvement of the mesolimbic dopamine system in depression was discussed (Nestler and Carlezon, 2006) and it was shown that alterations of key proteins of the ventral tegmental area/nucleus accumbens-axis produced behavioural phenotypes in rodents which are related to depression. As clear effects of spermidine and spermine on mesolimbic, but not striatal, dopamine-mediated behavior were observed (Hirsch et al., 1987), it is tempting to speculate that a dysregulation of the polyamine system could be causally involved with mesolimbic dopamine behaviour in depression. Thus, by now compelling evidence exists supporting that polyamines may be multifactorially involved with the manifestation of major depressive disorder.

In order to better understand the diverse brain specific functions of polyamines in health and disease, not only the regional but also the cellular and subcellular distribution of these potent modulators of neural functions has to be taken into account. Given the complexity and interconnectivity of brain circuits, the involvement of the polyamine system has to be analyzed accordingly. Immunocytochemically, spermidine/spermine (Laube et al., 2002; Laube and Veh, 1997) as well as agmatine (Otake et al., 1998) distribution were investigated in the rodent brain. Notably, while spermidine/spermine, although present in distinct neuronal populations, was predominantly localized to astrocytes, agmatine was not observed in glial cell bodies but in neurons. However, in untreated animals, agmatine was only localized to cortical and subicular neurons. Only after blocking axonal transport by colchicine, many more neuronal cell bodies were observed. Under these conditions, agmatine was most prominently detected in the diencephalon, namely thalamic, epithalamic, and hypothalamic regions. The distribution pattern of agmatine-like immunoreactivity in neocortical neurons was not characteristically showing principal neurons but rather interneurons, although this aspect was not investigated. In the hippocampus, however, labelled cell bodies were apparently very rare. While with spermidine/spermine immunocytochemistry, also neuropil areas were clearly labelled, agmatine immunoreactivity, even in non-colchicine-treated animals, was confined to cell bodies. In a subsequent investigation (Reis et al., 1998), however, using a different, commercial antibody, which was unfortunately not clearly specified, agmatine was localized to hippocampal CA1 pyramidal cells and axons and axon terminals in the stratum radiatum, mostly in contact with dendritic spines and associated with synaptic vesicles. The latter finding was discussed in support of the presumed function of agmatine as a neurotransmitter.

Neuronal spermidine/spermine labelling was most prominently observed in hypothalamic neurosecretory nuclei and in some motor and somatosensory areas (Laube et al., 2002). Regarding the widespread but not generalized localization of spermidine/spermine in astrocytes, it was hypothesized that astrocytes could supply the extracellular space with spermidine/spermine concentrations sufficiently high to account for NMDA receptor modification (Laube and Veh, 1997). The high concentration of spermidine/spermine in astrocytes does not necessarily mean that these polyamines have been synthesized in the very same cells. Indeed, the existence of several transport mechanisms for polyamines in neurons and glial cells (Masuko et al., 2003) may account for a redistribution away from synthesizing

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cells, e.g. by the action of organic cation transporters (Higashi et al., 2014). Further support for the assumption of an intercellular translocation of polyamines could be expected from the localization of polyamine pathway enzymes. In fact, ODC, the first polyamine anabolic enzyme which was investigated in this respect ((Cintra et al., 1987); reviewed in (Bernstein and Muller, 1999)) is normally found in neurons, thus supporting the assumption that astrocytic spermidine/spermine may reflect an uptake mechanism rather than endogenous synthesis. Considering other, similar tasks of astrocytes like the buffering of excess extracellular potassium, an effective polyamine uptake seemed reasonable with respect to a presumed neuromodulatory role and regarding the extracellular binding sites on NMDA receptors. In fact, both, an NMDA-mediated release of spermidine and spermine in rat striatum (Fage et al., 1992) and a membrane potential-dependent spermidine/spermine transport in synaptosomes and glial cells (Masuko et al., 2003) were demonstrated. In order to prove an efficient uptake of polyamines by astrocytes, we performed experiments using biotinylated spermine (Veh and Weiss, unpublished data). Acute slices of different rat brain areas were incubated in the presence of biotinyl-spermine at different concentrations and for different time intervals. Afterwards, the slices were chemically fixed and immunocytochemically investigated using the ABC technique to detect biotin and anti-spermidine/spermine antibodies to detect spermine, thus allowing to discriminate biotinylated and non-biotinylated spermine. These experiments clearly showed that already within 15 minutes biotinylated spermine was robustly detected in astrocytes, an effect that could be blocked by incubation in the presence of excess non-haptenylated spermine, thus indicating a specific uptake. Moreover, the uptake was shown to be less effective under depolarizing potassium conditions (30 mM potassium for 10 minutes).

ODC immunocytochemistry in brain provided the first evidence that the localization of polyamine pathway enzymes may essentially contribute to our understanding of brain specific roles for polyamines in certain cell types or circuitries. However, the presumed synthesis of putrescine from ornithine by ODC in certain types of neurons only reveals where the second step in the classical pathway of polyamine synthesis, starting from the amino acid arginine, is robustly expressed. Since ODC is highly inducible and normally ODC levels are tightly controlled, the observed labeling patterns may only reflect a subset of competent brain cells. Also, it could not be predicted whether ODC-expressing neurons would also synthesize the downstream products spermidine and spermine and also whether the alternative pathway via agmatine may be important in order to supply putrescine for polyamine synthesis in the brain. Thus, localization data covering the whole set of polyamine anabolic and catabolic enzymes would supply a screening framework, allowing to identify brain specific roles in health and disease and also targets for pharmacological intervention. To this end, we started to generate polyclonal antibodies against bacterial recombinant proteins for the anabolic enzymes spermidine synthase, spermine synthase, arginase, arginine decarboxylase, ornithine decarboxylase, and agmatinase and for the catabolic enzymes polyamine oxidase (PAOX), spermine oxidase (SMOX), and spermidine spermine acetyl transferase (SSAT). To date, we characterized the sera against spermidine synthase (Krauss et al., 2006; Krauss et al., 2007), spermine synthase, arginase (Peters et al., 2013), arginine decarboxylase (Peters et al., 2013), and agmatinase (Bernstein et al., 2011; Bernstein et al., 2012) and used them to immunocytochemically investigate these enzymes in rat and partially also in human (agmatinase) brain, with the exception of spermine synthase antibodies, that only worked with biochemical but not immunocytochemical techniques. In the literature, additional immunocytochemical data covering ODC, arginase, arginine decarboxylase, and SSAT are available. As it is beyond the scope of this review to systematically evaluate all available data on polyamine pathway enzyme localization in the brain, we will instead focus on a few examples, underlining the potential of this approach to help investigating the diverse roles of polyamines in the central nervous system.

As already mentioned, ODC was localized to subsets of neurons in several brain areas, although ODC expression is altered under pathological conditions (Bernstein and Muller, 1999), e.g. by appearing in astroglia. By contrast, the entry enzymes to both pathways of polyamine synthesis, arginase and arginine decarboxylase, leading to putrescine, spermidine, and spermine via arginase and to agmatine via arginine decarboxylase, turned out to be broadly and robustly expressed in all types of neurons (Iyo et al., 2006; Peters et al., 2013; Yu et al., 2003). Although the labelling in both cases was prominent in cell bodies, also a diffuse neuropil labelling was observed when using standard immunoperoxidase protocols. We therefore used a highly sensitive catalyzed reporter deposition (CARD)-based method (Madai et al., 2012), in order to visualize immunoreactivity distant from the soma. With this method, it became obvious that arginase and arginine decarboxylase, as well as previously shown for agmatinase (Madai et al., 2012), are broadly represented in the neuropil of cerebral cortex and hippocampus by numerous small punctate profiles (Peters et al., 2013), strongly suggestive of a synaptic distribution of these enzymes, which was not necessarily expected before. With electron microscopy, it was then resolved, that the immunoreactive spots correspond to labelled presynapses (arginase) and postsynapses (arginine decarboxylase). By comparison, agmatinase was localized to both, pre- and postsynaptic compartments. While the localization of arginase and arginine decarboxylase in synapses was rather surprising, the situation was clearly different with agmatinase, since agmatine is discussed as a putative neurotransmitter and hence a degradation of this polyamine at synapses would effectively control synaptic transmission. In contrast to arginase and arginine decarboxylase, agmatinase was frequently but less broadly detected in rat brain neurons (Bernstein et al., 2011; Peters et al., 2013). Here, agmatinase was especially prominent in the thalamic paraventricular nucleus and the medial habenula as well as in the main input and output areas of the medial habenula, the triangular septum and the interpeduncular nucleus. Since the medial habenula is also involved with stress-related phenomena (Sugama et al., 2002),

which, as mentioned earlier, in turn may be related to depression, we therefore selected this area to investigate the involvement of agmatine with electrical activity (Weiss, unpublished data) using extracellular single unit recording in acute brain slices. Neurons of the medial habenula showed spontaneous action potential firing. Upon superfusion with 2mM agmatine, the firing frequency was significantly reduced but returned to normal values after washing. The detailed analysis, however, showed that this overall inhibitory effect resulted from a mixed population of about 70% inhibition and 30% excitation, thus agmatine differentially affects action potential firing of medial habenular neurons. Since agmatine is an endogenous ligand for the imidazoline receptor, we tested the pharmacological effects of imidazoline receptor agonists and antagonists on spontaneous activity of neurons within the medial habenula. Briefly, the agonist moxonidine mimicked inhibitory agmatine-effects in the medial habenula, while the I1-type antagonist efaroxan, in contrast to the I2-type antagonist idazoxan, prevented the suppressive agmatine-effects. Furthermore, the α2-receptor antagonist yohimbine did not influence the agmatine-mediated modulation of firing frequencies in the medial habenula. Although currently no pharmacological tools are available to address the role of agmatinase in this area, the data show that the localization of the catabolic enzyme agmatinase successfully identified a brain target that certainly is worth investigating in the context of depressive disorders. To this end, the subnuclear organization of the medial habenula as well as the circuitry within the triangular septum/interpeduncular nucleus axis will have to be taken into account.

With respect to the identification of brain areas possibly relevant in the context of polyamine-influenced events, also the prominent localization of agmatinase in the thalamic paraventricular nucleus (Bernstein et al., 2011) has to be emphasized, since this nucleus was shown to be intimately involved with the regulation of stress and negative emotional behaviour, such as anxiety (Hsu et al., 2014). The paraventricular thalamic nucleus is strongly connected with the amygdala, bed nucleus of stria terminalis, and the nucleus accumbens shell, where it regulates the dopaminergic system. The involvement of the mesolimbic dopamine system with depression and polyamines was already mentioned above. However, the role of agmatine in the paraventricular thalamic nucleus has not been investigated so far. Interestingly, in the nucleus accumbens shell, we previously observed a patch-like spermidine synthase expression, overlapping with dopamine D1 receptor expressing patches (Krauss et al., 2007), indicating an involvement of spermidine/spermine in this circuitry, supporting the already mentioned data showing an involvement of spermidine/spermine with mesolimbic dopamine-mediated behavior (Hirsch et al., 1987).

Among polyamine pathway enzymes analyzed so far, spermidine synthase most clearly displayed a synaptic expression, already visible with standard immunoperoxidase labelling, in the cerebellar cortex (Krauss et al., 2007). Here, the giant mossy fibre terminals in the granule cell layer robustly displayed spermidine synthase immunoreactivity. We therefore chose this area to experimentally verify spermidine-mediated effects using electrophysiological methods (Krauss et al., 2007). Briefly, using extracellular recording upon mossy fibre stimulation, we found that spermidine bath application dose-dependently reduced field potential activity in this area, thus providing evidence for a polyamine-mediated modulation of mossy fibre synaptic transmission.

These examples may show, that the localization of polyamine pathway enzymes, especially when considering the possible redistribution of polyamines by transport processes, offers a valuable tool to identify brain areas and circuitries influenced by these multi-functional polycations as putative targets in order to develop strategies for pharmacological intervention. Therefore, we strongly believe that, especially in the context of major depressive disorder, polyamine-related research may lead to new therapeutic strategies.

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