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Review

Modulation of learning and memory by natural polyamines

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ABSTRACT

Spermine and spermidine are natural polyamines that are produced mainly *via* decarboxylation of L-ornithine and the sequential transfer of aminopropyl groups from *S*-adenosylmethionine to putrescine by spermidine synthase and spermine synthase. Spermine and spermidine interact with intracellular and extracellular acidic residues of different nature, including nucleic acids, phospholipids, acidic proteins, carboxyl- and sulfate-containing polysaccharides. Therefore, multiple actions have been suggested for these polycations, including modulation of the activity of ionic channels, protein synthesis, protein kinases, and cell proliferation/death, within others. In this review we summarize these neurochemical/neurophysiological/morphological findings, particularly those that have been implicated in the improving and deleterious effects of spermine and spermidine on learning and memory of naïve animals in shock-motivated and nonshock-motivated tasks, from a historical perspective. The interaction with the opioid system, the facilitation and disruption of morphine-induced reward and the effect of polyamines and putative polyamine antagonists on animal models of cognitive diseases, such as Alzheimer's, Huntington, acute neuroinflammation and brain trauma are also reviewed and discussed. The increased production of polyamines in Alzheimer's disease and the biphasic nature of the effects of polyamines on memory and on the NMDA receptor are also considered. In light of the current literature on polyamines, which include the description of an inborn error of the metabolism characterized by mild-to moderate mental retardation and polyamine metabolism alterations in suicide completers, we can anticipate that polyamine targets may be important for the development of novel strategies and approaches for understanding the etiopathogenesis of important central disorders and their pharmacological treatment.

Contents

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1. Overview of polyamines

1.1. Brief history

The history of polyamines began with the first microscopic observations of the human semen by van Lewenhoek who reported, in 1677, the presence of crystals in these samples after several days of standing [161]. In 1878, Schreiner identified those crystals as phosphate derivatives of an organic base. This base was subsequently named "spermine" because of the source from which it was initially isolated. However, the precise chemical composition and structure of the base remained unclear, and its correct structure was determined only in 1924, when Dudley et al. isolated spermine from bovine brain [79]. Notwithstanding, a basic compound named "neuridine" was isolated from brain tissue in 1885, by Krieger. This compound was subsequently found to be identical to spermine [78]. Two interesting and more detailed reviews of the history of polyamine research were published by Shaw [266] and Bachrach [12].

1.2. Structure

Polyamines are simple aliphatic amines [110]. Putrescine (1,4-diaminobutane), a diamine often misclassified as a polyamine, spermidine [*N*-(3-aminopropyl)-1,4-diaminobutane] and spermine [bis-*N*-(3-aminopropyl)-1,4-diaminobutane] are constituted by respectively one, two or three carbon chains, connected by nitrogen atoms (Fig. 1). They are water-soluble, have low molecular weight and a strongly basic character, due to the presence of amino groups [140,265,293,110]. Although polyamines are present in prokaryotic and eukaryotic cells, from plants and animals [294], the only polyamines synthesized by mammals are spermidine and spermine from the diamine putrescine [310].

Putrescine: $H_2N\text{-}(CH_2)_4\text{-}NH_2$

Spermidine: $H_2N\text{-}(CH_2)_3\text{-}NH\text{-}(CH_2)_4\text{-}NH_2$

Spermine: $H_2N\text{-}(CH_2)_3\text{-}NH\text{-}(CH_2)_4\text{-}NH\text{-}(CH_2)_3\text{-}NH_2$

Fig. 1. Structure of polyamines.

1.3. Metabolism

1.3.1. Synthesis and transport

The amino acid ornithine is the major precursor of endogenous polyamines. In the brain, ornithine is formed mainly from the hydrolytic cleavage of the amino acid arginine in a reaction catalyzed by arginase [261,328,51]. Ornithine is decarboxylated by ornithine decarboxylase (ODC), the limiting enzyme in the polyamine synthesis, to putrescine, which is the immediate precursor for the synthesis of spermidine and spermine. The synthesis requires an aminopropyl group, which is provided by S-adenosylmethionine (SAM) decarboxylase, and spermidine synthase, a transferase that transfers the aminopropyl group of SAM to putrescine, generating spermidine. Spermine synthase catalyzes the transfer of a second group aminopropyl to spermidine, forming spermine [287,303,153,218,221]. The deficiency of spermine synthase is associated with the Snyder–Robinson syndrome, a X-linked mental retardation disorder [49]. The affected males present decreased spermine synthase activity and low levels of intracellular spermine in lymphocytes and fibroblasts with corresponding increased spermidine/spermine ratios. The clinical picture includes mild-to-moderate mental retardation, hypotonia, cerebellar dysfunction, seizure predisposition, facial asymmetry, thin habitus, osteoporosis and kyphoscoliosis [49]. The polyamine biosynthesis pathway is reversible, *i.e.* spermine can be converted to spermidine and putrescine. The first step of interconversion is the acetylation of spermine or spermidine in the position N1, catalyzed by the enzyme spermine/spermidine acetyltransferase (SSAT) which uses acetylCoA as acetyl donor. After this step, the acetylated polyamine undergoes oxidative breakdown, by action of polyamine