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Pegg A E & McCann P P. Polyamine metabolism and function. *Amer. J. Physiol.* 243:C212-21, 1982.
[Department of Physiology, Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, PA and Merrell Dow Research Center, Cincinnati, OH]

This brief review describes the reactions responsible for the biosynthesis and interconversion of polyamines in mammalian cells, the regulation of cellular polyamine content, and the importance of polyamines in the cell cycle, cell division, tissue growth, and differentiation. The availability of specific inhibitors of the polyamine biosynthetic pathway and their potential as research tools and pharmacological agents are also discussed. [The *SCI*® indicates that this paper has been cited in over 415 publications.]

Anthony E. Pegg
Department of Physiology
Milton S. Hershey Medical Center
Pennsylvania State University
Hershey, PA 17033

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My interest in polyamines dates back to 1967, shortly after I joined H. Guy Williams-Ashman's laboratory as a postdoctoral fellow. He suggested that we attempt to clarify the biochemical reactions responsible for the biosynthesis of polyamines in mammalian cells. Although the biosynthetic pathway forming polyamines in *Escherichia coli* had been described by S.M. Rosenthal, C.W. Tabor, and H. Tabor, there was at that time little information on polyamine synthesis in eukaryotes.

Our first reports described the characterization of ornithine decarboxylase[1] and the putrescine-activated S-adenosylmethionine decarboxylase[2] from rat prostate. Both decarboxylases are highly regulated, showing significant increases in activity in response to a wide range of growth-promoting stimuli, and they have therefore been the subject of numerous reports. Interestingly, our paper that first described the enzyme 5'-methylthioadenosine phosphorylase,[3] which degrades the 5'-methylthioadenosine that is also produced in the polyamine biosynthetic reactions, was hardly quoted at all for several years. However, starting some 10 years later, reports of more extensive purifications of the enzyme appeared, and the work has since been cited more frequently.

The review of polyamine metabolism and function that is the subject of this article was suggested in 1982 by Howard Morgan. He had recently taken over as editor of the cell physiology section of the *American Journal of Physiology* and was eager to broaden the journal's base of submissions; in particular, he wanted to increase the coverage of factors regulating cell growth. The tremendous increase in interest in polyamines over the preceding few years resulted largely from the availability of potent and specific inhibitors of ornithine decarboxylase, whose synthesis and usefulness as pharmaceutical agents and biochemical research tools were pioneered by a group of scientists at Merrell International (now Merrell Dow Research Institute) led by A. Sjoerdsma. I was most fortunate in being able to persuade one of the key figures in this program, Peter P. McCann, to coauthor the review with me. His intimate knowledge of this work was of paramount importance in putting together an up-to-date and comprehensive review.

There are a number of reasons that this work has been so widely quoted in a relatively short time. The polyamine field has continued to thrive and expand exponentially. Almost all of the studies have used, either directly or indirectly, inhibitors such as α-difluoromethylornithine (eflornithine) and have involved one or another of the enzymes in the biosynthetic pathway. Early work with these inhibitors and the key features of the biosynthetic enzymes are described succinctly in our review, and many of these papers have used it as a citation covering a large number of key references. Our review also provided investigators with a concise summary of the biochemical and physiological background necessary to these studies. Another factor was the considerable interest in therapeutic use of α-difluoromethylornithine, which is clearly a valuable drug in the treatment of the African trypanosomes that cause sleeping sickness and of *Pneumocystis carinii* pneumonia occurring in conjunction with AIDS.[4] It also has some potential use against a variety of other diseases caused by parasitic protozoa and diseases characterized by deranged cellular proliferation including psoriasis and neoplasia.

A more recent overview of polyamine physiology that describes much of the biochemical and molecular biological work accomplished in this area since our review appeared last year.[5] A book containing chapters covering all aspects of the design of polyamine biosynthesis inhibitors and their use by many of the leaders in these fields has been published recently.[6]

Finally, the page numbers of our review have been given incorrectly in about 10 percent of the citations. This is partly due to the anachronistic page numbering of the *American Journal of Physiology*, which uses letters as well as numbers. The letters are quite frequently ignored by the citing authors.

1. **Pegg A E & Williams-Ashman H G.** Biosynthesis of putrescine in the prostate gland of the rat. *Biochemical J.* 108:533-9, 1968. (Cited 315 times.)
2. ————. On the role of S-adenosylmethionine in the biosynthesis of spermidine by rat prostate. *J. Biol. Chem.* 244:682-93, 1969. (Cited 360 times.)
3. ————. Phosphate-stimulated breakdown of 5'-methylthioadenosine by rat ventral prostate. *Biochemical J.* 115:241-7, 1969. (Cited 110 times.)
4. **Sjoerdsma A, Golden J A, Schechter P J, Barlow J L R & Santi D V.** Successful treatment of lethal protozoal infections with the ornithine decarboxylase inhibitor, α-difluoromethylornithine. *Trans. Assn. Amer. Physicians* 97:70-9, 1984.
5. **Pegg A E.** Recent advances in the biochemistry of polyamines in eukaryotes. *Biochemical J.* 234:249-62, 1986.
6. **McCann P P, Pegg A E & Sjoerdsma A,** eds. *Inhibition of polyamine biosynthesis: biological significance and basis for new therapies.* Orlando, FL: Academic Press, 1987. 371 p.

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