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Russell D H & Snyder S H. Amine synthesis in regenerating rat liver: extremely rapid turnover of ornithine decarboxylase. *Mol. Pharmacol.* 5:253-62, 1969.
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In regenerating rat liver, the activity of ornithine decarboxylase increased 20- to 30-fold in a very short time suggesting a rapid enzyme turnover. Enzyme turnover rate was estimated by measuring the decline in activity after administering inhibitors of protein synthesis such as cycloheximide or puromycin. With both enzyme inhibitors, ornithine decarboxylase activity declined very rapidly with a half-life of about 11 minutes. [The *SCI*® indicates that this paper has been cited in over 400 publications.]

A Most Rapidly Turning Over Mammalian Enzyme

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Diane H. Russell was my first postdoctoral fellow, and so, when she arrived in 1967, I sought for her a research project that could provide exciting results, hopefully in a short time frame. I was interested in histamine biosynthesis and had just observed that gastrin induced histidine decarboxylase in the stomach with a half-life for enzyme turnover of about 2 hours.[1] I was fascinated by reports from George Kahlson's laboratory in Lund of increased histamine synthesis in rapidly growing tissues such as fetal rat liver, suggesting a link of histamine to growth processes.[2] But Kahlson had found exceptions, rapidly growing tissues, such as regenerating rat liver, in which histidine decarboxylase activity was not altered. I wondered if some diamine other than histamine, perhaps putrescine or cadaverine, might be implicated in these cases. One could readily measure decarboxylation of almost any amino acid, because ^{14}C-carboxyl labeled derivatives of the major amino acids were commercially available so that one could merely monitor $^{14}CO_2$ evolution.

With great energy and enthusiasm, which for years thereafter became her trademark, Diane learned how to conduct partial hepatectomy operations in rats, ordered the amino acids, and, less than a week after joining the lab, conducted her first experiments. I remember well watching the emerging scintillation counter tape. With amino acid after amino acid, there were very few counts of $^{14}CO_2$ with no difference between control and partially hepatectomized rats. When we got to ornithine, the control samples had about 40 cpm, while the regenerating liver samples "went crazy" with the dial racing to about 2,000 cpm.

In a few months, Diane characterized the extraordinary increase in ornithine decarboxylase activity of regenerating rat liver.[3] She also showed very high levels in rapidly growing tumors, chick embryo, and after treatment with growth hormone.[4]

The 10- to 50-fold increases in ornithine decarboxylase activity less than an hour after stimulation might have involved activation of preexisting enzyme protein rather than new protein synthesis. To explore this question, Diane pretreated animals with actinomycin D to inhibit RNA synthesis, and with puromycin or cycloheximide, to inhibit protein synthesis. All three drugs blocked the induction of ornithine decarboxylase. Most strikingly, treatment of control rats or rats with regenerating livers with either puromycin or cycloheximide produced a very rapid decline in enzyme activity with a half-life of about 11 minutes.

In the late 1960s, enzyme induction was a particularly hot area. The most rapidly turning over mammalian enzymes, such as delta-aminolevulinic acid synthetase, tyrosine transaminase, and tryptophan pyrrolase, had half-lives of one and one-half to two hours, and most other enzymes had half-lives measured in days. Thus, ornithine decarboxylase was far and away the most rapidly turning over mammalian enzyme at the time.

The high citation rate of this paper probably relates to the importance of ornithine decarboxylase as a regulated enzyme protein influencing tissue growth that, to this day, is extensively studied.[5]

I dropped out of polyamine research when Diane left the lab, while she made it the focus of her professional career and became a world leader. This past year she died tragically of cancer. The world of science has lost a much valued, immensely talented contributor.

1. **Snyder S H & Epps L E.** Regulation of histidine decarboxylase in rat stomach by gastrin: the effect of inhibitors of protein synthesis. *Mol. Pharmacol.* 4:187-95, 1968. (Cited 60 times.)
2. **Kahlson G & Rosengren E.** New approaches to the physiology of histamine. *Physiol. Rev.* 48:155-96, 1968. (Cited 270 times.)
3. **Russell D & Snyder S H.** Amine synthesis in rapidly growing tissues: ornithine decarboxylase in regenerating rat liver, chick embryo, and various tumors. *Proc. Nat. Acad. Sci. USA* 60:1420-7, 1968. (Cited 915 times.) [See also: **Russell D H.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life.* Philadelphia: ISI Press, 1986. p. 147.]
4. **Russell D H, Snyder S H & Medina V J.** Growth hormone induction of ornithine decarboxylase in rat liver. *Endocrinology* 86:1414-9, 1970. (Cited 145 times.)
5. **Pegg A E.** Recent advances in the biochemistry of polyamines in eukaryotes. *Biochemical J.* 234:249-62, 1986. (Cited 320 times.)

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