

Biological Role of Carnosine in the Functioning of Excitable Tissues

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Centenary of Gulewitsch's Discovery

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Carnosine was discovered by W. S. Gulewitsch in 1900 [1]. During this time, biochemistry entered the period when the inventory of the constituents of the living cell had been started. Hence, the publication of Gulewitsch and Amiradzibi (in *Ber. Deutsch. Chem. Ges.*) on a dipeptide from muscle extract was not a big sensation.

The years have passed. Biochemists have discovered many new natural compounds that were sooner or later mapped to a certain position in metabolic pathways. Only carnosine and its methylated derivative anserine (term suggested by Accerman), which was independently described by Gulewitsch and Tolkachevskaya and named "galin" (this name did not stick), remained unmapped.

Gulewitsch did not live long enough to see the discovery of the function of the muscle dipeptides, and he left this problem to his disciple S. E. Severin, who devoted most of his long life in science to the solution of this problem. It was Severin who in 1953 described the first clear functional response of the muscle to carnosine. He showed that isolated frog muscle significantly longer preserves excitation-induced response when carnosine is present in the medium. In the presence of carnosine, the muscle can accumulate enormous amounts of lactate without obstruction, but in the absence of carnosine lactate causes dramatic acidification of the tissue, thus inducing contraction. [2].

In 1938, Bate Smith [3] noticed that the pK values of carnosine (6.9) and anserine (7.1) indicate that these compounds are ideal buffers at physiological pH. He also demonstrated that 40% of the buffer capacity of fast twitch muscle is due to these dipeptides. The rest of the buffer capacity is mainly due to the muscle proteins, most of which are immobilized, unlike the mobile dipeptides. This is especially important considering the mobile

pH buffer-assisted (and immobilized buffer-suppressed) mixing of local pH gradients inside the large and highly structured muscle cell [4].

Surprisingly, by the end of his life, Severin did not acknowledge that he had discovered the function of carnosine [5]. He thought that the buffer role of these dipeptides is too small and insignificant for the compounds that he had studied for so many years. His opinion was not changed even by the publication of Effron et al. who showed that the phenomenon described by Severin in his muscle experiments is reproduced when Tris buffer substitutes for carnosine [6].

Recent publications (many of which are brilliantly reviewed by the authors of this issue) unequivocally indicate that apart from the pH-buffering role, carnosine and anserine have a number of other functions (another confirmation of the principle of polyfunctionality of biological compounds). Carnosine and anserine are also antioxidants, metal-complexing agents, and protectors of proteins from modification. Sometimes they act as neuromediators. In fact, carnosine is the first and the simplest representative of neuropeptides, which are important signal components in the animal body. Hence, Severin was not very wrong when he skeptically reacted to my attempts to persuade him that in 1953 he discovered the intracellular pH-buffering function of carnosine. The real state of the art is significantly more complex for sure.

Nevertheless, pH buffering may be the main function in muscle, i.e., in the tissue where carnosine was discovered a century ago by W. S. Gulewitsch. It is the pH-buffering function that is the best explanation for the high concentration of the histidine-containing dipeptides in the tissue where acidification limits the major functional work.

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