An update on carnosine and anserine research

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Carnosine belongs to a family of histidyl dipeptides, consisting of L-histidine and beta-alanine. It is more prevalent in the mammalian and human tissues, whereas its analogues such as anserine, which is methylated at the N_π of imidazole, is present in birds and fish and balenine, methylated at the N_ε of histidine, is largely present in marine mammals and reptiles (Boldyrev et al. 2013). Despite their early discovery and their prominent concentrations in certain tissues, the exact role and potential of these dipeptides are still not fully understood. Carnosine is a multifunctional dipeptide. Based on its biochemical properties, it has been suggested to be involved in acid–base balance, antioxidant defense and scavenging of lipid peroxidation products. The latter functions of the dipeptide have generated various expectations as therapeutic interventions, e.g. for the pathologies associated with enhanced generation of lipid peroxidation products.

There is a growing interest from the broad scientific community to unravel the fundamental properties as well as the potential application spectrum of carnosine and related dipeptides. As to date (December 2018), over 3300 publications are found on Web of Science when searching for ‘carnosine’, and Fig. 1 displays the fundamental (panel A) and applied research areas (panel B) in which these papers are mostly situated. The majority of fundamental research

is performed in the field of biochemistry/molecular biology, pharmacology and physiology (Fig. 1a). The major application fields are neurology, diabetes, cardiovascular disease and nutrition (Fig. 1b), although the interest and relevance are broad and extends all the way to agriculture, zoology, sports sciences, etc. The wide variety of disciplines of the manuscripts in this current Special Issue is a reflection hereof.

In the field of diabetes, the interest in carnosine as a therapeutic target for obesity, types 1 and 2 diabetes and its complications was stimulated by the discovery of the carnosinase gene as a risk factor for diabetic nephropathy (Janssen et al. 2005). The present issue contains two valuable original contributions that follow-up on this finding. Rodriguez-Niño et al. (2019) explore the relevance of urinary carnosinase excretion in relation to renal function in type 2 diabetics, while Baye et al. (2019) expand their findings on the first carnosine supplementation trials in obese individuals (De Courten et al. 2016). A major hurdle in carnosine supplementation studies is the low stability and bioavailability of carnosine due to high presence of serum carnosinase in humans. Two manuscripts of this special issue propose to deal with this pharmacological challenge: Qiu et al. (2019) develop and identify a novel selective carnosinase inhibitor, carnostatine. On the other hand, Everaert et al. (2019) explore the pharmacokinetics of an alternative approach by supplementing anserine, a natural analogue of carnosine, which is somewhat more resistant to hydrolysis by carnosinase.

Although the potential therapeutic applications of carnosine are broad, current research is intensified on pathologies relating to tissues with a natural abundance of the histidine-containing dipeptides, such as the myocardium. In this special issue, two novel pathophysiological mechanisms of carnosine in cardiac myocytes are uncovered by Nelson et al. (2019) and Zhao et al. (2019). Nelson et al. (2019) characterize a novel detoxification pathway mediated by carnosine, which forms conjugates with catecholaldehydes, which are pathologically reactive catecholamines metabolites generated in the myocardium. Similarly, Zhao

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Fig. 1 Number of published scientific papers, retrieved by a Web of Science search on ‘carnosine’ (topic), divided by general scientific discipline (**a**) and by applied scientific discipline (**b**) Source: Clarivate analytics (analysis on September 19th, 2018)

et al. (2019) provide direct evidence how carnosine could protect the adult cardiomyocytes from toxic lipid peroxidation products, generated during ischemia–reperfusion injury and heart failure. The pleiotropic action of carnosine implies therapeutic potential in various diseases, including cancer and neurodegeneration. The contribution by Oppermann et al. (2019) describes a novel level of complexity by suggesting carnosine’s influence on epigenetic regulation in glioblastoma cells. Berezhnoy et al. (2019) review the role of carnosine as a neuromodulator and neuroprotector.

Apart from the various ongoing therapeutic research lines, there remains a vast interest in the normal physiological role in carnosine-rich tissues, such as skeletal muscle. Spelnikov and Harris (2019) use published experimental data to develop a kinetic model to describe carnosine

synthesis in human skeletal muscle. Yet, one of the most surprising findings published in this special issue comes from Nagai et al. (2019) showing that carnosine in skeletal muscle sensitizes afferent autonomic nerves from skeletal muscles and thus for the first time suggest that the large intracellular carnosine pool in skeletal muscle cells may also serve extracellular signaling functions.

Although the role of carnosine abundance in skeletal muscle has attracted some research interest over the past century, the attention was intensified in the last decade after the discovery by Harris et al. (2006) showing that chronic dietary intake of beta-alanine can increase human muscle carnosine concentration and thereby improve exercise capacity. Three papers in this issue expand on this observation. Bassinello et al. (2019) compare three modes of muscle

contraction (isometric, isotonic and isokinetic) to better characterize the strength potentiation of carnosine loading. Da Silva et al. (2019) elaborate on the energy delivery systems during exercise that are affected by beta-alanine supplementation. Finally, the optimal dietary mode of the actual beta-supplementation regimen is investigated by Varanoske et al. (2019).

The current special issue contains 12 valuable original contributions and 1 review paper, delivering exciting new insights and representing considerable research progress. However, they also identify a significant remaining gap in our understanding and application of carnosine and related dipeptides. Therefore, we hope that this initiative will inspire and attract more researchers to help unravel the enigmatic role of carnosine and related dipeptides; a journey that started nearly 120 years ago, with the discovery of the dipeptide in 1900 by Gulewitch (Boldyrev et al. 2013).

The special issue was composed on the occasion of and written by attendants of the fifth International Congress on Carnosine and Anserine (ICCA) which was held from 12th to 14th of September 2017, at the Diabetes and Obesity Center, University of Louisville (Dr. Shahid P. Baba and colleagues). It is endorsed by the Carnosine Consortium (http://users.unimi.it/carnosine_co/), after previous successful meetings in Moscow (2000), Ghent (2011), Tokyo (2014) and Gabicce Mare (2015). Approximately 80 researchers from all the continents gathered for an exciting 3-day conference, dedicated to the topic of carnosine and related dipeptides. The Carnosine Consortium is a common forum for the basic understanding and applications of histidyl dipeptides. This conference formally helps coalesce both established and young investigators working on disparate aspects to interact and develop a coherent view in understanding these dipeptides. A similar special issue in this journal was previously published in 2012 following the Ghent meeting (Derave and Sale 2012).

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Compliance with ethical standards

Conflict of interest We have acknowledged the financial support provided for the organization of the Conference.

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