

openheart β -Alanine and orotate as supplements for cardiac protection

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CARNOSINE: ACID BUFFER, ANTIOXIDANT AND AID TO MUSCLE CONTRACTION

β -Alanine is a rate-limiting precursor for synthesis of the dipeptide carnosine (β -alanyl-L-histidine), which is produced within and stored in high concentrations in skeletal muscle, heart and olfactory receptor neurons.^{1 2} β -Alanine supplementation has been shown to boost the carnosine content of skeletal muscle.³ This reflects the fact that the K_m of carnosine synthase for β -alanine (in excess of 1 mM) is far higher than the β -alanine content of tissues; its K_m for histidine is two orders of magnitude lower, such that intracellular histidine levels are not rate-limiting for carnosine synthesis.³ β -alanine is produced in the liver during catabolism of uracil; after its release to plasma, it can be transported into tissues that require it for carnosine synthesis. Plasma levels of β -alanine also increase when carnosine is ingested in flesh foods; particularly in humans, carnosinase activity in plasma rapidly cleaves carnosine to its precursors β -alanine and histidine.⁴ The pK_a of the imidazole ring of carnosine is 6.83, which makes it an ideal physiological buffer for tissues when glycolytic production of lactic acid is high.³ (The pK_a of free histidine's imidazole ring is around 6, so converting histidine to carnosine makes it a more effective buffer.) Most studies with supplemental β -alanine have focused on skeletal muscle and athletic performance; many studies have concluded that β -alanine supplementation can both boost muscle carnosine content and aid performance in high-intensity anaerobic workouts in which lactic acid is generated, presumably by preventing counterproductive reductions in intracellular pH.³ The fact that carnosine concentrations in fast-twitch muscles are higher than those in slow-twitch muscles is consistent with this paradigm.

Carnosine also has versatile antioxidant activity, likewise reflecting the properties of its imidazole ring. This can serve efficiently as an electron donor, preventing lipid peroxidation; it also quenches singlet oxygen and interacts with superoxide in a way that stabilises it.^{5 6}

Like histidine, carnosine can chelate copper and iron, and this chelation prevents these ions from catalysing Fenton chemistry, hence blocking production of hydroxyl radicals.⁵ Moreover, carnosine-copper complexes possess superoxide dismutase activity.⁷ Further, carnosine binds covalently to reactive degradation products of peroxidised lipids, preventing them from reacting with other cellular targets.⁸

Carnosine may also function in skeletal muscle and heart to amplify the impact of cytoplasmic calcium on muscular contraction.^{9 10} It seems to do so by sensitising the contractile apparatus to free calcium; some, but not all, studies suggest that it also can upregulate calcium release from the sarcoplasmic reticulum.

BOOSTING CARDIAC CARNOSINE AS A STRATEGY FOR CARDIOPROTECTION

Cardiac muscle manufactures carnosine and related derivatives of histidine; most of these are *N*-acetylated.^{11 12} The intracellular levels of these histidine derivatives in cardiac muscle is about 10 mM, likely reflecting a key need for their buffering activity when oxygen availability fails to meet the need for ATP production and glycolytic lactic acid production compensatorily increases. Moreover, the versatile antioxidant activity of carnosine and related histidine compounds produced in the heart also seems likely to be cardioprotective.^{13 14} Indeed, exogenous carnosine has been shown to protect cardiac tissue from ischaemia-reperfusion damage, and is also protective for doxorubicin-induced cardiomyopathy.^{15–21} Further, the procontractile impact of carnosine would be of potential value in congestive failure.

It is reasonable to suspect that supplemental β -alanine would boost cardiac stores of carnosine and *N*-acetylcarnosine, although studies documenting this do not appear to be available. This follows from the fact that the K_m for β -alanine of carnosine synthetase—known to be expressed in cardiac muscle, albeit at a lower level than in skeletal



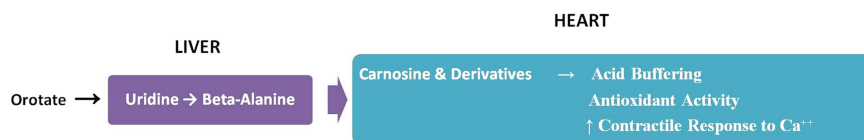
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Figure 1 Cardioprotective potential of orotate.



muscle²²—is above 1 mM; although it is difficult to find studies that have measured heart β -alanine levels, the level of other free amino acids in the heart is in the low micromolar range.²³ Moreover, β -alanine released by the liver or supplied from the diet should have access to cardiomyocytes, since it is carried across membranes by the taurine transporter, vital for cardiac function.^{24 25} Given carnosine's antioxidant, acid-buffering and procontractile activities, dietary measures that boost cardiac levels of carnosine and *N*-acetylcarnosine could be expected to be protective in disorders such as myocardial infarction, angina and congestive failure; however, the extent to which this would be of clinical significance remains to be clarified. With respect to the acid-buffering activity of carnosine and its derivatives, it is pertinent to note that the clinical utility of carnitine in cardiac ischaemia may be largely attributable to its ability to promote mitochondrial oxidation of pyruvate, hence lessening glycolytic generation of lactic acid.²⁶

To date, clinical studies evaluating the utility of supplemental β -alanine or carnosine in cardiac disorders appear to be lacking. However, dietary β -alanine presupplementation in rats subsequently subjected to 45 min of left main coronary occlusion was found to be associated with a 57% reduction in infarct size to risk area ratio.²⁷ Although the authors attributed this effect to moderate taurine depletion of the heart induced by the high β -alanine intake (3% in drinking water), they did not consider the possible role of carnosine and *N*-acetylcarnosine in this phenomenon.

OROTATE AS A CARNOSINE PRECURSOR

Of possible pertinence is an intriguing literature documenting that supplemental magnesium orotate is clinically useful in congestive failure and angina.^{28–31} In particular, a placebo-controlled study evaluating magnesium orotate (6 g daily for 1 month, 3 g daily for 11 months) in patients with severe congestive failure, reported a 75.7% survival rate in the orotate treated patients, as opposed to 51.5% survival in those receiving placebo ($p < 0.05$).³¹ Orotates are also beneficial in a hamster model of inherited cardiomyopathy.³² The explanation typically offered for the utility of this agent in cardiac conditions is that the stressed heart benefits from an increased pool of pyrimidine nucleotides; oral orotate is taken up by the liver and is converted to uridine, some of which reaches the plasma and can be taken up by cardiac tissue.^{28 33} The magnesium in this complex is also thought to benefit the failing heart.³⁴ But why pyrimidines should be so beneficial to the heart has never been clear. This explanation is somewhat

difficult to square with the observation that orotic acid supplementation only transiently and modestly increases the pyrimidine pool in the heart, yet it aids contractile recovery after global ischaemia and prevents loss of adenine nucleotides.³³ Perhaps the difficulty in explaining the basis of orotate's protective activity has resulted in this important research receiving less attention than it deserves.

As an alternative or additional explanation, it should be noted that absorbed orotate is ultimately converted to β -alanine. After orotate is employed in uridine synthesis in the liver,^{33 35} uridine is eventually broken down to yield free uracil. The catabolism of uracil involves its successive conversion to dihydrouracil, β -ureidopropionate and β -alanine.^{36 37} This β -alanine can then serve as a precursor for synthesis of carnosine in the skeletal muscle, the brain and the heart³⁸ (see figure 1). Hence, supplementation with mineral orotates or orotic acid may represent a practical strategy for boosting the level of carnosine and carnosine derivatives within the body. Moreover, orotate may be viewed as a 'delayed release' form of β -alanine that may be better tolerated than β -alanine itself. Ingestion of β -alanine in doses greater than 800 mg at one time is often associated with 'pins and needles' paraesthesias that can last for about an hour, coinciding with an elevation of plasma β -alanine; the basis of this effect is obscure.^{3 39} Orotate supplementation, even in very high doses, does not seem to be attended by this problem, likely because the evolution of β -alanine proceeds gradually after orotate ingestion (timed-release β -alanine preparations can also be used to cope with this problem⁴⁰).

These considerations suggest that supplemental β -alanine should be evaluated in experimental and clinical cardiac disorders, and that the role of carnosine in the documented protective effects of orotates in such conditions should be assessed. Also, since the heart makes a range of histidine derivatives other than carnosine, it would be interesting to know whether supplemental histidine might impact the cardiac level of some of these. Intriguingly, there is recent evidence that supplemental histidine may be beneficial in metabolic syndrome.⁴¹

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