Ischemia-Reperfusion Injury and Melatonin

To the Editor:

It was with great interest that we read the recently published article by Ruiz-Meana et al[1] regarding the pathophysiology of myocardial damage due to ischemia-reperfusion and new treatment options for acute myocardial infarction (AMI). The authors should be congratulated on their up-to-date information. However, we wanted to stress that there are experimental mechanistic data that establish a cause-effect relationship between the production of oxygen free radicals and their pathophysiological role as a possible treatment target for AMI.

When blood flow is restored in ischemic hearts, it produces oxygen-derived free radicals such as the superoxide anion, hydroxyl radicals, and hydrogen peroxide, which can damage cell membranes.[2] The 3 principal mechanisms for damage by free radicals are lipid peroxidation, protein oxidation, and DNA breakage or alteration. Superoxide radicals can generate hydroxyl radicals by 2 methods. One involves the participation of nitric oxide through the formation of a compound named peroxynitrite, a toxic, unstable, and highly reactive compound causing lipid peroxidation and myocardial damage.[2]

Melatonin is an indolamine principally produced, with a circadian rhythm, by the pineal gland. It regulates various physiological and neuroendocrine functions through specific receptors or directly in subcellular organelles.

Their actions were initially described relative to the neuroendocrine-reproductive axis.[3] However, numerous observations made at later dates have demonstrated its multiple immunomodulating functions, on both the cellular and humoural levels, and its antioxidant activity.[4]

Numerous clinical studies in humans have revealed a relationship between melatonin serum concentration and coronary artery disease.[4] The observation that patients with coronary disease have low nocturnal melatonin levels and that concentrations in AMI patients is lower than in control subjects shows that this nocturnal drop in melatonin is at least partly due to its antioxidant effects, and particularly its ability to act as an

interceptor of free radicals that are generated in the first hours of an AMI.[5] However, it is unknown to date if this finding is a cause or effect of, or even a characteristic related to, diminished cardiovascular function.[4] Two possible mechanisms have been described which could explain the antioxidant effects of melatonin in AMI patients: *a)* due to direct action as a free radical interceptor, detoxifying reactive forms of oxygen and nitrogen through non-enzymatic channels, which would result in the formation of another powerful antioxidant: N_1-acetil-N_2-formil-5-metoxiquinuramina; and *b)* by way of an indirect action mechanism through stimulation of various antioxidant enzymes and the stabilisation of membrane fluidity.[6]

Due to its antioxidant and anti-inflammatory properties, melatonin has been shown to have beneficial results and a significant protective effect in various experimental models of reperfusion injury.[4] Experimental results have contributed solid evidence for considering melatonin to be one of the essential components of an organism's antioxidant defence system.[4] The available scientific evidence has led our group to carry out a phase II clinical trial to demonstrate inhibition of reperfusion damage by administering melatonin to AMI patients immediately before percutaneous coronary intervention.[7] Melatonin is an endogenous molecule with few side effects and a low monetary cost. Its lipophilic nature allows it to cross cell membranes with ease to reach cell compartments where oxygen-derived free radicals can be found.

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REFERENCES

1. Ruiz-Meana M, Garcia-Dorado D. Fisiopatología del daño miocárdico por isquemia-reperfusión: nuevas oportunidades terapéuticas en el infarto agudo de miocardio. Rev Esp Cardiol. 2009;62:199-209.
2. Férez Santander SM, Márquez MF, Peña Duque MA, Ocaranza Sánchez R, de la Peña Almaguer E, Eid Lidt G. Daño miocárdico por reperfusión. Res Esp Cardiol. 2004;57 Supl 1:9-21.
3. Reiter RJ. Pineal melatonin: cell biology of its synthesis and of its physiological interactions. Endocr Rev. 1991;12:151-80.
4. Reiter RJ, Tan DX. Melatonin: a novel protective agent against oxidative injury of the ischemic/reperfused heart. Cardiovasc Res. 2003;58:10-9.
5. Domínguez-Rodríguez A, Abreu-González P, García M, Sánchez J, Marrero F, Armas-Trujillo D. Decreased nocturnal melatonin levels during acute myocardial infarction. J Pinel Res. 2002;33:248-52.
6. Reiter RJ, Tan DX, Manchester LC, Qi W. Biochemical reactivity of melatonin with reactive oxygen and nitrogen species: a review of the evidence. Cell Biochem Biophys. 2001;34:237-56.
7. Domínguez-Rodríguez A, Abreu-González P, García-González MJ, Kaski JC, Reiter RJ, Jiménez-Sosa A. A unicenter, randomized, double-blind, parallel-group, placebo-controlled study of Melatonin as an Adjunct in patients with acute myocaRdial Infarction undergoing primary Angioplasty The Melatonin Adjunct in the acute myocaRdial Infarction treated with Angioplasty (MARIA) trial: study design and rationale. Contemp Clin Trials. 2007;28:532-9.

Response

To the Editor:

We are very honoured by the interest that Drs Domínguez and Abreu have shown in our article on the physiopathology of myocardial reperfusion.[1] In their letter, the authors describe the possible cardioprotective effects of melatonin, which is a treatment approach that was not mentioned in our article. The reason for this omission was that given limited space, it was simply impossible to list all of the cardioprotective treatments that have been shown to be effective in experimental models; we only included those for which the experience is more solid, or the cardioprotective mechanism better-known. We do recognize, however, that melatonin is of special interest due to being an endogenous molecule that can be used in humans, and which is probably safe. Regarding its action mechanism, we feel that it is not completely clear. In their letter, Domínguez and Abreu attribute the mechanism to melatonin's antioxidant and anti-inflammatory properties. We would like to make 2 comments on this topic. Firstly, we feel that most important protective effect that can be expected in preventing damage by free radicals is the prevention of mitochondrial permeability transition.[1,2] Some studies show that this could be true for melatonin.[3] However, recent data indicate that these cardioprotective effects of melatonin could be mediated by receptors and could depend on the cyclic guanosine monophosphate channel, which is a signal channel shown to be very important for different cardioprotective strategies.[4,5]

We wish Drs Dominguez and Abreu success with their phase II study, and we will await their results with great interest.

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REFERENCES

1. Ruiz-Meana M, García-Dorado D. Fisiopatología del daño miocárdico por isquemia-reperfusión: nuevas oportunidades terapéuticas en el infarto agudo de miocardio. Rev Esp Cardiol. 2009;62:199-209.
2. Ruiz-Meana M, Abellán A, Miró-Casas E, García-Dorado D.

Opening of mitochondrial permeability transition pore induces hypercontracture in Ca2+ overloaded cardiac myocytes. Basic Res Cardiol. 2007;102:542-52.
3. Jou MJ, Peng TI, Reiter RJ, Jou SB, Wu HY, Wen ST. Visualization of the antioxidative effects of melatonin at the mitochondrial level during oxidative stress-induced apoptosis of rat brain astrocytes. J Pineal Res. 2004;37:55-70.
4. García-Dorado D, Agulló L, Sartorio CL, Ruiz-Meana M. Myocardial protection against reperfusion injury: The cGMP pathway. Thromb Haemost. 2009;101:635-42.
5. Genade S, Genis A, Ytrehus K, Huisamen B, Lochner AJ. Melatonin receptor-mediated protection against myocardial ischaemia/reperfusion injury: role of its anti-adrenergic actions. Pineal Res. 2008;45:449-58.