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Melatonin protects heart and brain*

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INTRODUCTION

The Royal Society of South Africa has a noble heritage that challenges us today (Carruthers, 2008). Our Society is potentially a major forum for peer appraisal in science: prestigious, individual and quality orientated. It is claimed to be the meeting ground of people who not only share their knowledge, but debate it, question it, appreciate it, and who are dedicated to advancing it. To achieve these noble aims, we were modelled on the Royal Society of London that had been born at the right moment, in the early 1660s, for the growth of science in Britain. In that Royal Society, debates around scientific purpose, direction, organisation and management had remained priority aims from the start.

Reality was far from those noble ideals. 1666 was the year not only of the Great Fire of London, but of intellectual hot waters. Isaac Newton described how a prism split up light into different colours of different wave lengths. He showed that the light was not modified, but during the passage through the prism the rays physically separated. How was this simple truth received by Fellows of the Royal Society in 1666? One of the influential Fellows was Robert Hooke, a famous physicist of Hooke’s Law fame. He saw the views of Newton as scientific blasphemy.

With maximal disdain, Newton complained: “I was so persecuted from the publication of my theory of light ….” Not until Hooke’s death did Newton become President of the Royal Society in 1703. Thus Newton had a mere wait of 37 years to be fully recognized by the Royal Society. So much for the early traditions of the Royal Society, showing that any really novel ideas may initially meet with resistance that might sometimes be emotional as well as scientific. Thus it is with some diffidence we will argue with others for the positive protection of heart and brain by melatonin, extending beyond its well-known sleep-promoting properties.

HYPOTHESIS: MELATONIN PROTECTS BOTH HEART AND BRAIN

The proposed evolutionary background to our hypothesis is as follows. Going back to when hominids were evolving several million years ago, it seems totally improbable that the cardioprotective molecular paths that we and others have been studying, were evolved to protect from heart attacks which were totally unknown. Rather, we have hypothesized that those evolving hominids had to be protected from blood loss in hunting (Opie et al., 2010). More recently, perhaps about 130,000 years ago, a Pleistocene skull showed signs of interpersonal altercation, probably caused by blunt force trauma, showing that humans had to escape not only from wild animals but from their fellows (Wu et al., 2011). We further hypothesize that such causes of blood loss would have affected not only the heart but other vital organs including the brain. Thus we may expect to find similar protective paths in the heart and brain. Overall, we and others have been impressed by many similarities between the molecular paths acting by the same molecules that protect major organs from the consequences of low blood flow (ischaemia).

These paths are found not only in the heart but also in other major organs, namely the brain, kidneys and liver (Opie & Lecour, 2011). There are messages of mutual interaction and protection that travel between these major organs to invoke the same protective molecular pathways in these vital but very diverse organs of the human body (Hausenloy & Yellon 2008). Hence, what is cardioprotective may also be brain protective, a hypothesis. This hypothesis is here explored in relation to the effects of melatonin, which is a naturally occurring compound found in animals, plants and microbes. In humans, the daily circadian rhythms of the circulating levels of melatonin regulate sleep patterns.

MELATONIN AND CARDIOPROTECTION

If heart and brain share some protective mechanisms (Opie & Lecour, 2011), then it is appropriate briefly first to review the protective mechanisms whereby melatonin acts on the heart before considering effects on the brain. Melatonin has a relatively complex chemical structure and is one of several cardioprotective compounds found in red wine (Opie & Lecour, 2007). Thus, the cardioprotective qualities of wine do not reside only in the alcohol content. Cardioprotection can also be elicited by low alcohol red wine, reducing the alcohol content from 12% to 6%, which did not alter its antioxidant and cardioprotective properties (Lamont et al., 2012).

*Based on a talk given to the Royal Society of South Africa

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Our group has tested the cardioprotective effects of melatonin on model heart attacks (Lamont et al., 2011). These were produced by tying off the major coronary artery in isolated perfused rat hearts, thereby severely restricting the coronary flow normally bringing oxygen to the heart and causing substantial myocardial cell death, technically called myocardial infarction (as in experiments by Yellon and Hausenloy, see white areas in Figure 1, top panel) (Lamont et al., 2011). When the coronary flow was restored after 30 min by releasing the ligation, and followed by reperfusion, the size of the zones of dead tissue was diminished (similar to the smaller white areas in Figure 1, middle panel). We found that the prior addition of melatonin, in the range of human physiological levels (Klupiniska et al., 2006; Hickie & Rogers, 2011), to the perfusion fluid of these isolated hearts resulted in smaller infarct sizes (similar to cardioprotection shown in the lower panel of Figure 1). We also used STAT-3 knock-out rats to show that the protective molecular mechanism was by stimulation of the SAFE (Survivor Activator Factor Enhancement) pathway. Other workers have reported that such reductions in infarct size are mediated by decreased calcium ion penetration into damaged mitochondria (Petrosillo et al., 2009, 2010), and by the anti-adrenergic properties of melatonin (Genade et al., 2008). Overall, melatonin has complex pleiotropic signalling mechanisms (Hardeland, 2009), including stimulation of a path that is also protective in the heart, namely the phosphatidylinositol-3-kinase/Akt path, also called the RISK path (Genade et al., 2008; Hausenloy et al., 2009; Nduhirabandi et al., 2011).

In both model heart attacks and in strokes, flooding of the mitochondria with calcium through the “gateway” in the mitochondrial membrane is the proposed crucial lethal molecular event that kills the heart or brain cells damaged by severe restriction of blood flow (Opie & Lecour, 2011). This gateway that controls the crucial intramitochondrial calcium concentrations is the mitochondrial permeability transition pore (mPTP). In the heart, calcium-induced mPTP opening that is associated with an elevated release of cytochrome C occurs with aging (Petrosillo et al., 2010). These detrimental changes are counteracted by melatonin, possibly by limiting the age-related rise in harmful oxidized cardiolipin.

**WIDER CARDIOPROTECTIVE PROPERTIES OF MELATONIN**

Intra-coronary melatonin increases coronary blood flow and cardiac function through β-adrenergoreceptors, melatonin receptors, and via formation of nitric oxide in anaesthetized pigs (Grossini et al., 2011). Chronic melatonin consumption by prediabetic rats prevented obesity-related metabolic abnormalities and protected the heart against myocardial ischaemia and reperfusion injury in a model of diet-induced obesity (Nduhirabandi et al., 2011). Thus, carrying the analogy between heart and brain further, besides the possible specific effects of melatonin on heart mitochondria, there could also be a wider range of beneficial effects of melatonin on the brain.

**MELATONIN PROTECTS THE BRAIN**

In the brain, melatonin is not only synthesized by the pineal gland, but it acts on various brain sites including the hippocampus and the corpus striatum. Experimentally, melatonin decreased the size of model brain strokes (Andrabi et al., 2004). Melatonin (10 mg/kg intraperitoneal) or vehicle was given at occlusion and reperfusion of the middle cerebral artery. Furthermore, melatonin improved the respiratory rate in the cortex, hypothalamus and the corpus striatum (Dragicevic et al., 2011). As in the heart, loading of the mitochondria with calcium ions through the opening of the controlling “gateway”, the mPTP, is the proposed crucial lethal molecular event that kills the brain cells already damaged by severe restriction of blood flow (Andrabi et al., 2004). Also, as in the case of the heart, the brain can also be subject to conditioning, albeit using different time intervals from those used in cardiac experiments (Kitagawa, 2012). For example, resveratrol, quanosine, and losartan can protect the brain by differing molecular signalling pathways. Some of the signalling paths involved have been explored (Paradies et al., 2010). The proposal is that melatonin opposes the adverse oxidation of cardiolipin, the phospholipid located at the level of inner mitochondrial membrane. Melatonin is selectively taken up by mitochondrial membranes, a function apparently not shared by other antioxidants (Srinivasan et al., 2011).

**Figure 1.** The concept of reperfusion lethal injury as described by Yellon and Hausenloy (2007). Cross-sections were taken from isolated perfused coronary-ligated rat hearts. The top panel shows a large white area of dead non-perfused tissue, surrounded by a small area of viable red tissue. The middle panel shows increases in viable perfused red tissue and a decreased amount of dead white tissue. The bottom panel shows further improvement by prior cardioprotection, achieved by preconditioning with only a small residual area of dead white tissue. In the panel on the right, similar principles hold for isolated mice hearts (data from Lamont et al., 2010). Figure adapted from Yellon & Hausenloy (2007), with permission.
Inhibition of the mPTP of brain cells decreased cytochrome c release with less activation of the intramitochondrial potentially lethal enzyme caspase-3 (Andrabi et al., 2004). Furthermore, direct proof of an effect of melatonin on the mitochondrial transition pore was that melatonin strongly inhibited currents mediated by this pore in a dose-dependent manner. The concentration used inhibited 50% of the peak activity (IC50) at 0.8 micromole/L (Andrabi et al., 2004), which is in a concentration range about 1,000 times higher than the peak circulating melatonin levels found in humans at night (Hickie & Rogers, 2011).

It needs to be emphasised that the concentrations or the doses of melatonin used in these and several other cerebroprotective experiments (Andrabi et al., 2004) have, in general, far exceeded those that could be regarded as physiologically relevant. However, in two neuronal cell lines, physiological concentrations of melatonin (1 nM) regulated the expression of the antioxidant enzyme genes for glutathione peroxidase and superoxide dismutases at the mRNA level (Mayo et al., 2002). Furthermore, the same low concentrations of melatonin concomitantly increased the life-time of these mRNAs (Mayo et al., 2002). Similar lower melatonin concentrations should be tested by other workers.

**MELATONIN AND ALZHEIMER’S DISEASE**

In a mouse model of Alzheimer’s disease, melatonin directly protected brain mitochondria (Dragicevic et al., 2011). Melatonin also is a strong antioxidant (Mayo et al., 2002; Paradies et al., 2010; Nduhirabandi, et al., 2011; Srinivasan et al., 2011). Melatonin has thus been viewed as a potential therapeutic tool for treating neurodegenerative disorders such as Alzheimer’s disease, and for preventing the lethal effects of brain ischaemia/reperfusion. In advanced Alzheimer’s disease, brain biopsies show solid-looking plaques of congealed protein, the amyloid-beta (Aβ) peptide plaques. Following the intracerebral injection of fibrillar-Aβ into aged Wistar rats, there is an adverse intracellular amyloid cascade of cell degeneration. Melatonin reverses some of these alterations found in experimental Alzheimer’s disease and protects mitochondrial membranes from microscopic damage (Rosales-Corral et al., 2012a,b). More specifically, intracerebral injection of fibrillar-Aβ induces alterations in mitochondrial membrane phospholipids and increases the levels of mitochondrial membrane phosphatidyl serine values substantially. Melatonin reduces these high levels of phosphatidyl serine to below control values (P < 0.05). Furthermore, melatonin increases the levels of the cerebroprotective omega-3 linolenic and eicosapentaenoic acids in the brain sites where amyloid-β was injected, which may provide an additional cytosolic molecular protective pathway.

There may also be other unexplored effects of melatonin on the brain. As the brain can also be preconditioned, albeit using different time intervals from the heart (Kitagawa, 2012), it would be reasonable to postulate that melatonin might also activate the preconditioning paths in the brain. It is already known that resveratrol (Shin et al., 2012), guanosine (Dal-Cim et al., 2012), and losartan (Liu et al., 2012) can protect the brain by various molecular signalling pathways.

**POTENTIAL CLINICAL CEREBROPROTECTIVE APPLICATIONS OF MELATONIN AND AGOMELATINE**

Can melatonin be clinically applied to treat Alzheimer’s disease in patients? The problem is that Alzheimer’s disease is a highly complex disease of multifactorial causation (Rosales-Corral et al., 2012a,b) so that any single therapeutic agent such as melatonin might have less clinical effect than expected. Regarding the role of melatonin in mood depression, agomelatin, a melatonin-receptor agonist and selective serotonin receptor subtype (5-HT2C) antagonist, is under study (Hickie & Rogers, 2011) This agent acts differently from the standard antidepressants, such as the serotonin uptake inhibitors, by stimulating melatonin receptors. Besides antidepressant effects, patients treated by agomelatine have experienced improved quality of sleep and reduced waking during the night (Hickie & Rogers, 2011). Reverting to the role of melatonin in experimental cerebroprotection, as previously discussed, it may be predicted that agomelatine should also protect from mitochondrial damage in various cerebral diseases and lessen the damage of vascular disease. These hypotheses have yet to be tested.

From the evolutionary point of view, survival benefit could have been achieved by basic protective molecular mechanisms that could give multiorgan protection from traumatic events such as acute blood loss. There are many similarities between such molecular paths acting by the same molecules that protect major organs from the consequences of low blood flow (ischaemia). These paths are found not only in the heart but also in other major organs, namely the brain, kidneys and liver. Melatonin, a hormone physiologically made by the pineal gland, has experimental cardioprotective and cerebroprotective qualities. Thus melatonin, in concentrations similar to the peak circulating values found in humans, protected isolated hearts from cell death provoked by coronary occlusion and reperfusion. Melatonin in much higher concentrations protected brain cells from death in model strokes, probably by decreasing the adverse effects of excess calcium ions on the mitochondrial permeability transition pore. However, melatonin has not been tested in clinical trials in human cardiac or cerebral disease. The melatonin receptor stimulator, agomelatine, is a currently available pharmacological agent that might hypothetically help to explore the potentially cerebroprotective effects of melatonin stimulation in human cerebrovascular disease.

**REFERENCES**


