Editorial comment to: Mehmet Erol Yildirim et al. Melatonin protects kidney against apoptosis induced by acute unilateral ureteral obstruction in rats. Cent European J Urol. 2016; 69: 225-230.

The multiple biological action potential of melatonin – is melatonin, mitochondria and the ischemic /reperfusion injury relationship essential in the pathogenesis of obstructive nephropathy?

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Melatonin is known to have a multiple biological action potential. Melatonin and several of its metabolites have been shown to act as an antioxidant and cytoprotective agent by reducing the oxidative stress by acting as a free radical scavenger [1], and also by activating several antioxidant systems [2]. Melatonin is originally defined as an agent which reduces lipid peroxidation and scavenges reactive oxygen species which usually initiate lipid peroxidation [3]. Furthermore , melatonin has potent antioxidant properties [4]. Melatonin stimulates antioxidant enzymes (e.g. glutathione peroxidase, glutathione reductase, etc.) and suppresses oxidative enzymes (lipoxygenase and nitric oxide synthase). It is believed that melatonin can protect the mitochondria and exert strong anti-apoptotic effects [5]. In a current study, Yildirim et al. showed that melatonin significantly reduces the apoptotic scores occurring after acute unilateral ureteral obstruction in a kidney rat model [6]. However, the authors did not observe a return to normal histological features in the obstructed kidneys.

In general, obstructive uropathy leads to tubular damage (atrophy) due to apoptosis induction. Impaired urine flow can cause increased accumulation of reactive oxygen species and environmental changes favoring pro-apoptotic factors within the kidney. A wide range of intrarenal factors can stimulate intense fibrosis. Progressive fibrosis with overproduction of extracellular matrix proteins (e.g. collagen, fibronectin, etc.) is a key process in kidney function deterioration. These proteins are accumulated in the tubulointerstitium leading to further renal impairment. Urethral obstruction affects proper renal blood flow and glomerular filtration rate due to the increased pressure in the Bowman's capsules of the nephrons. In consequence, this leads to the overactivation of the renin-angiotensin system. Angiotensin II induces transforming growth factor-beta, which causes the overproduction of extracellular matrix proteins.

Lipid peroxidation induced by free oxygen radicals leads to cell membrane damage via the degradation of polyunsaturated fatty acids of membranes and the loss of its integrity and cell lysis [7]. This fact may partly explain the lack of return to normal histological features in the obstructed kidneys presented in the Yildirim et al. study. Cell death has been divided into two types: programmed cell death (apoptosis) and accidental cell death (necrosis). Mitochondria are unique cell organelles which present with highly dynamic activity, in which they are constantly elongating and dividing to form a network. The dynamic nature of the mitochondrial networks is due to two opposing processes, mitochondrial fission and fusion, that operate concurrently. The fission and fusion processes are crucial for maintaining the mitochondrial function [8, 9]. Previous studies have shown that the mitochondria play a crucial role in the cell death process. The mitochondria release several proteins into the cytosol in response to the cell death which signal through the mitochondrial membrane permeabilization, triggering the activation of several cell death pathways. Mitochondria act as a node where cell death pathways are integrated and propagated, resulting in the release of pro-apoptotic factors from the mitochondria which induce massive activation

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of caspases and in turn activate a proteolitic cascade leading to cellular demise. Different factors which can activate the mitochondrial-dependent pathway of cell death (such a free oxygen radicals, DNA injury and gamma-radiation) are described [10]. Mitochondrial dysfunction is implicated in the etiology of various diseases (e.g neurodegenerative diseases, diabetes, cardiovascular disease, skeletal muscle disorders, etc.) [11]. Melatonin is a highly lipophilic substance that can cross cell membranes to easily reach subcellular compartments, including the mitochondria to where it seems to accumulate in high concentrations. Moreover, melatonin can interact with lipid bilayers and stabilize mitochondrial inner membranes [12]. As mentioned by Yildirim et al. in a current study, ischemia/reperfusion injuries in the kidneys are well known in the surgical era, but ischemia/reperfusion injury in obstructive nephropathy has not yet been extensively studied. It is well known, that the relationship between melatonin, mitochondria and ischemia/reperfusion is a common problem encountered in the clinic (e.g. liver surgery, liver transplantation, etc.). The pathogenesis of ischemia/reperfusion injury is multifactorial and includes the overproduction of free oxygen radicals. For example, the liver ischemia/reperfusion leads to the impairment of the hepatic mitochondrial function and energy metabolism. On the other hand, melatonin administration prior to the injury protects against mitochondrial dysfunction in the liver induced by the ischemia/reperfusion in the rat model.

In conclusion, further research is needed to clarify the relationship between the mitochondria, ischemia/reperfusion injury, melatonin and renal function. In the case of urine flow obstruction, this relationship will aid in better understanding the complex pathogenesis of obstructive nephropathy.

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