Hypertension Research (2013) 36, 682–683

www.nature.com/hr

COMMENTARY

Should melatonin be used to lower blood pressure?

Ehud Grossman

Hypertension Research (2013) **36,** 682–683; doi:10.1038/hr.2013.29; published online 18 April 2013

Ambulatory blood pressure monitoring in normotensive and hypertensive subjects demonstrates a dipping blood pressure (BP) circadian pattern with a 10% decrease in BP readings at night. Some patients demonstrate a decrease of <10% (non-dipping) or even an increase in BP at night (reverse dipping).[1] The diurnal BP pattern is an important factor in determining cardiovascular (CV) complications in hypertensive patients. An impaired nocturnal BP fall is associated with a high risk of developing target organ damage and CV morbid events.[2] A non-dipping pattern is observed in the elderly and in individuals with diabetes, sleep apnea syndrome, metabolic syndrome, orthostatic hypotension or several forms of secondary hypertension.[3] The mechanism responsible for the reduction in BP during sleep and the pathophysiological mechanism underlying a lack of this nocturnal fall remain unclear.

Melatonin is a hormone that is normally secreted by the pineal gland at night. It serves as the signal of darkness in humans and, as such, has a pivotal role in the physiological regulation of circadian rhythms, including sleep.[4] Evidence from the past 10 years suggests that melatonin may influence the CV system in humans.[4] Furthermore, exogenous melatonin has been shown to induce several hemodynamic effects in healthy men and women.[5]

It has been suggested that melatonin may have a role in the circadian rhythm of BP.[6] The study by Obayashi *et al.*[7] in this issue supports the hypothesis that a low nocturnal melatonin level is associated with a non-dipping pattern. The authors showed that non dippers have lower urinary nocturnal excretion of the main melatonin metabolite, 6-sulfatoxymelatonin (urinary melatonin excretion, UME), than do dippers. Unfortunately, the authors did not collect urine during the day time and therefore did not test for a lack of nocturnal increase in urinary UME in non dippers. The authors also did not evaluate the patients for secondary hypertension and did not exclude sleep apnea and orthostatic hypotension, all of which could explain non-dipping. Nevertheless, the observation of a low UME level during the night time in non dippers is solid and extends previously reported results.[6] It is noteworthy that a low nocturnal UME level did not affect sleep quality. Thus, sleep disturbances cannot explain the non-dipping BP pattern. These findings support previous observations and suggest that diminished melatonin production at night, together with normal day time production, has a role in the pathogenesis of non-dipping BP patterns.[6] The role of melatonin in the pathogenesis of hypertension has also been shown in several animal models of hypertension.[8]

If indeed melatonin deficiency has a role in the pathogenesis of nocturnal hypertension, then melatonin administration may lower BP at night. Several studies have evaluated the effects of melatonin on nocturnal BP.[5,9] The results were not consistent: in some studies, melatonin reduced nocturnal BP, whereas in others it did not reduce nocturnal BP or even increased it. Not all studies used the same melatonin formulation: some used controlled-release (CR) formulations, and others used fast-release (FR) formulations. We recently analyzed the data from all of these studies and found that the addition of CR melatonin to antihypertensive therapy is effective and safe in ameliorating nocturnal hypertension, whereas FR melatonin is ineffective. Melatonin is rapidly metabolized, with an elimination half-life of between 40 and 50 min.[10] Following oral administration of exogenous FR melatonin, peak plasma levels are reached at 20–30 min, are then maintained for 90 min and rapidly decline afterwards.[10] FR melatonin formulations are thus unable to provide melatonin for the second half of the night. CR formulations circumvent the fast clearance of the hormone and provide circulating melatonin profiles that more closely match the normal physiological release. Therefore, for exogenous melatonin to be present during the later part of the night, it must be administered via a controlled-release preparation or at very high doses.

Melatonin may lower nocturnal BP via several mechanisms (Figure 1). Vascular melatoninergic receptors have been identified and have been shown to be functionally linked with the vasoconstrictor or vasodilator effects of melatonin.[5] Other neurohormonal properties of melatonin such as sympathetic inhibition could also contribute to its cardioprotective effects.[5] Impaired nocturnal sympathetic suppression with sustained adrenergic activity during sleep has been reported in patients with nocturnal hypertension (non dippers).[5] Administration of melatonin may therefore contribute to the nocturnal suppression of the sympathetic nervous system. The reduction in the activity of the oxidative enzyme myeloperoxidase by melatonin may also contribute to the vasoprotective and BP-lowering effects of melatonin.[5] Melatonin may also directly dilate peripheral arteries,[5] thereby reducing peripheral resistance and leading to nocturnal BP fall. Moreover, melatonin has been shown to stimulate the release of tissue factor pathway inhibitor from the vascular endothelium, which may suppress thrombosis and arterial restenosis.[5]

It seems logical that melatonin should be considered as a pharmacological agent to control BP in non dippers and in individuals

E Grossman is at Department of Internal Medicine D and Hypertension Unit, The Chaim Sheba Medical Center (affiliated with Sackler School of Medicine, Tel-Aviv University), Tel-Hashomer, Israel.
Email: grosse@post.tau.ac.il

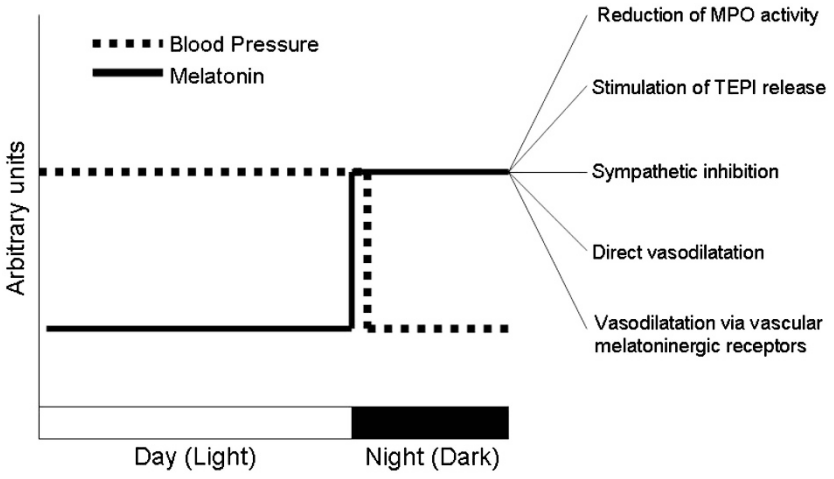

Figure 1 Circadian pattern of BP and melatonin and the possible mechanisms by which melatonin lowers BP. MPO, myeloperoxidase; TFPI, tissue factor pathway inhibitor.

with uncontrolled hypertension, especially in conjunction with conventional antihypertensive agents.

CONFLICT OF INTEREST

The author declares no conflict of interest.

1 Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. *N Engl J Med* 2006; **354**: 2368–2374.
2 Verdecchia P, Schillaci G, Gatteschi C, Zampi I, Battistelli M, Bartoccini C, Porcellati C. Blunted nocturnal fall in blood pressure in hypertensive women with future cardiovascular morbid events. *Circulation* 1993; **88**: 986–992.
3 Voichanski S, Grossman C, Leibowitz A, Peleg E, Koren-Morag N, Sharabi Y, Shamiss A, Grossman E. Orthostatic hypotension is associated with nocturnal change in systolic blood pressure. *Am J Hypertens* 2012; **25**: 159–164.
4 Brzezinski A. Melatonin in humans. *N Engl J Med*. 1997; **336**: 186–195.
5 Grossman E, Laudon M, Zisapel N. Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials. *Vasc Health Risk Manag* 2011; **7**: 577–584.
6 Jonas M, Garfinkel D, Zisapel N, Laudon M, Grossman E. Impaired nocturnal melatonin secretion in non-dipper hypertensive patients. *Blood Press* 2003; **12**: 19–24.
7 Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S, Ikada Y, Kurumatani N. Nocturnal urinary melatonin excretion is associated with non-dipper pattern in elderly hypertensives. *Hypertens Res* 2013; **36**: 736–740.
8 Leibowitz A, Peleg E, Sharabi Y, Shabtai Z, Shamiss A, Grossman E. The role of melatonin in the pathogenesis of hypertension in rats with metabolic syndrome. *Am J Hypertens* 2008; **21**: 348–351.
9 Grossman E, Laudon M, Yalcin R, Zengil H, Peleg E, Sharabi Y, Kamari Y, Shen-Orr Z, Zisapel N. Melatonin reduces night blood pressure in patients with nocturnal hypertension. *Am J Med* 2006; **119**: 898–902.
10 Waldhauser F, Waldhauser M, Lieberman HR, Deng MH, Lynch HJ, Wurtman RJ. Bioavailability of oral melatonin in humans. *Neuroendocrinology* 1984; **39**: 307–313.