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MELATONIN ENLARGES THE BLADDER WITHOUT AFFECTING THE BLADDER CONTRACTION PRESSURE OR THE ELECTROENCEPHALOGRAM FINDINGS: A COMPARISON BETWEEN YOUNG AND SENESCENT RATS

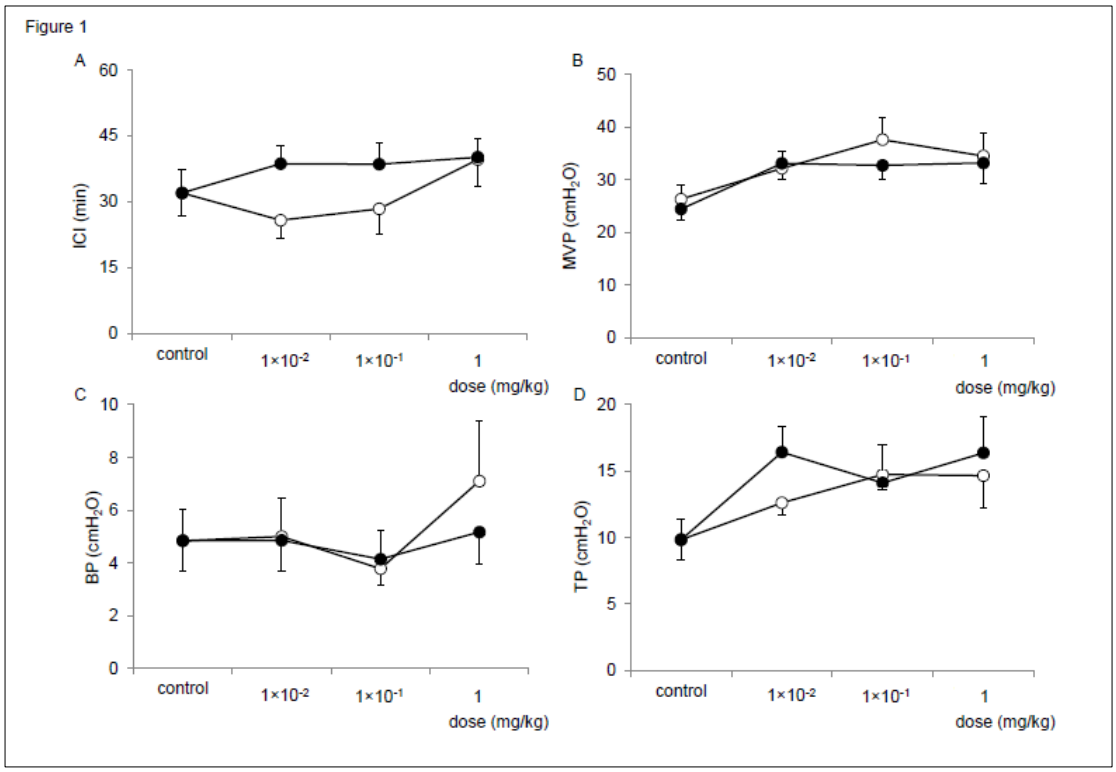
Hypothesis / aims of study
We propose diminished functional bladder capacity, polyuria, nocturnal polyuria and sleep disturbance as potential causes of nocturia. Melatonin is a prime determinant of circadian rhythms. Impaired production of melatonin with aging can be involved in the disruption of the normal circadian pattern of both sleep and micturition that leads to nocturia in older adults. The exogenous administration of melatonin has been reported to not only improve sleep disturbance, but also ameliorate nocturia. We carried out the present study to examine the effects of melatonin on bladder function and sleepiness, and to study changes in its effects with age.

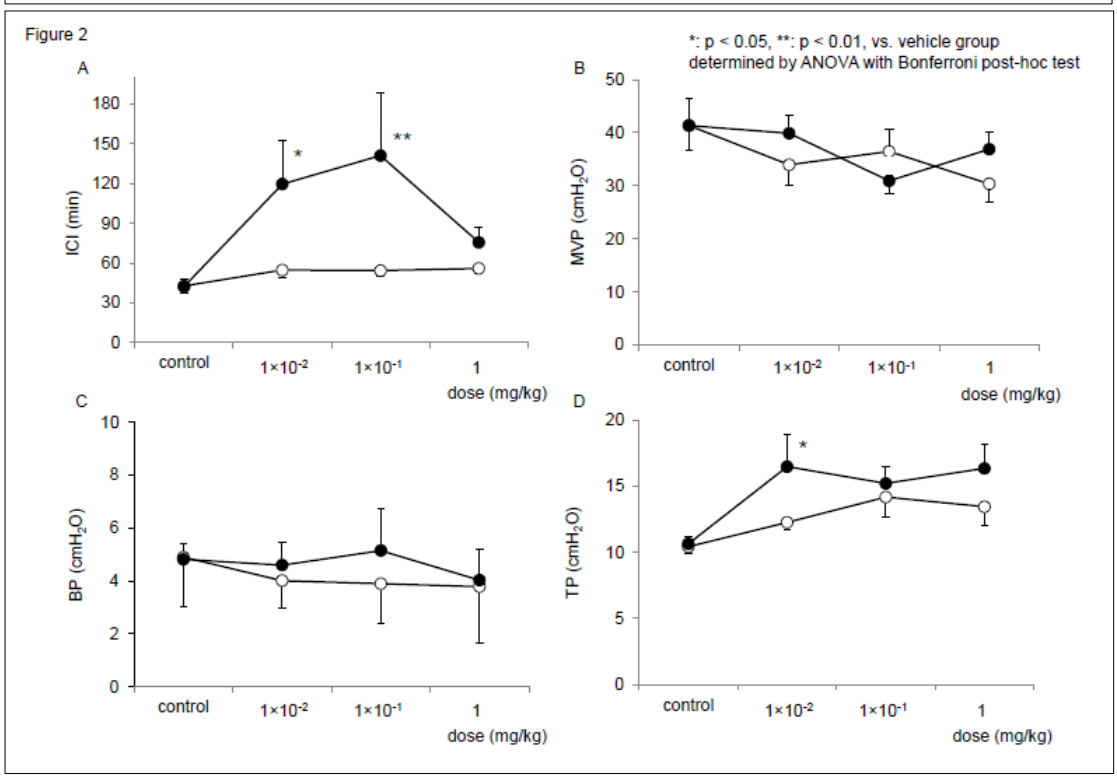
Study design, materials and methods
Ten-week-old and 24-month-old female Sprague-Dawley rats were used. Cystometrography and electroencephalography (EEG) were performed simultaneously on unanesthetized rats. We examined the effects of intravenous melatonin administration (1.0×10^{-2} – 1.0 mg/kg) on the cystometric parameters (intercontraction interval (ICI), micturition voiding pressure (MVP), basal pressure (BP), and pressure threshold (PT)) as well as the power value of the delta wave, which was measured as a marker of sleepiness, and compared results by age. The frequency and amplitudes of the delta wave were defined as 0.5-3.5 Hz and from 50 to more than 200 μV, respectively. Statistical comparisons were performed by repeated measures analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test. A level of $p < 0.05$ was considered statistically significant.

Results
Ten 10-week-old rats and 9 24-month-old rats were used. In the 10-week-old rats, melatonin did not affect ICI, MVP, BP or TP (Fig. 1 A-D). In the 24-month-old rats, however, melatonin significantly increased the mean ICI to 1.8 and 2.3 times as much as that in controls at doses of 1.0×10^{-2} and 1.0×10^{-1} mg/kg, respectively (versus vehicle group; $p = 0.020$ and $p = 0.004$, respectively; Fig. 2A). In the24-month-old rats, melatonin increased PT at a dose of 1.0×10^{-2} mg/kg (versus vehicle group; $p = 0.027$, Fig. 2D). There are no significant effects of melatonin on MVP or BP at any concentration (Fig. 2B-C). Additionally, melatonin show no significant effects on power value at either the storage or voiding phase in either group.

Interpretation of results
We previously reported that intracerebroventricular melatonin enlarges bladder capacity via the GABAA receptor rather than the melatonin MT1/MT2 receptor. [1] Thus, the ICI-elongation effect of melatonin is assumed to arise via the GABAergic system. With respect to this effect, which was seen only in senescent rats, we suggest the following interpretations. First may be due to the difference in administrating paths. Although peripherally administered melatonin can reach the brain, it may not reach a sufficient concentration to act. Second, it may be that peripherally administered melatonin acts as an antioxidant rather than as a receptor agonist. Thus, melatonin would affect older rats because they have suffered much more oxidative stress. Third, it may be that sensitivity to melatonin is particularly high in senescent rats. It has been reported that plasma melatonin levels in rats are lower in rats greater than 17 months. [2] Thus, the senescent rats in the present study may have lower plasma melatonin levels and therefore may have been especially susceptible to exogenous melatonin. In this study, melatonin did not significantly affect EEG parameters, possibly because the rats were examined under restraint and non-physiological conditions. It is also possible that melatonin might have only limited influence on EEG. In one report, 2.5 mg/kg of melatonin induced only limited effects on the EEG sleep parameters. [3] We used a maximum dose of 1 mg/kg, which may not have been sufficient for melatonin to affect EEG.

Concluding message
Melatonin increases only ICI without affecting MVP, BP, TP or EEG parameters in senescent rats; it did not affect young rats in the present study. Although our findings were obtained under limited conditions, they nevertheless suggest that melatonin may be beneficial for nocturia in the elderly.





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Disclosures

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