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INCREASING EFFECT OF SLEEP AND ITS DEPTH ON BLADDER VOLUME IN RAT

Aims of Study

A large amount of urine is usually stored in the bladder during sleep at night. This observation may suggest that bladder volume can be influenced by sleep. It is well known that various physiological changes during sleep (ex. blood pressure, pulse rate, basic metabolic rate, hormone secretion, autonomic nerve activity, muscle tone…etc) are coupled with the depth of sleep. However, the changes of vesicourethral function occurring during sleep have not yet been studied in detail. Thus, the present study evaluated whether a physiological sleep affects bladder volume by examining the 24 hour frequency/volume(F/V) characteristics of rat. In addition, we also studied the 24 hour F/V characteristics of rat by changing the depth of sleep with a widely used hypnotic, zolpidem tartrate(ZP).

Methods

16 SD adult rats (8 male;477±14.5g, 8 female;302±11.8g) were acclimatized for 7 days in individual metabolic cages with 12/12 hr light/dark cycle (light period starts at 7 a.m.) in a temperature- and ventilation-controlled room. After acclimatization, the recording of micturition parameters in each rat was carried out continuously for 6 consecutive days. The voided volume was measured by a digital balance placed below the metabolic cage. The balance was connected to a PC which stored the time and voided volume of each micturition by making a weight measurement every 10 seconds. In the first two days, the baseline micturition parameters were obtained without giving any drugs. At 7 a.m. (the beginning of light cycle) on the 3rd day, a 1 ml oral dose of water was administered. At 7 a.m. on the 4th day, 2mg/Kg of zolpidem tartrate (ZP) dissolved in 1ml of water was administered orally. On the 5th day, neither drug nor vehicle was given. At 7 p.m. (the beginning of dark cycle) on the 6th day, ZP was again administered orally. During the acclimatization period and following 6 days, the rats had free access to water and food. The amount of water imbibed was also monitored every day. Every 24 hours' measurement data of micturition from 6 days experiments was divided into two periods (light and dark) and analyzed separately. The values were compared using Student's t-test, with $p<0.05$ considered to be significant. The results were expressed as the mean±SEM.

(Experimental Protocol)

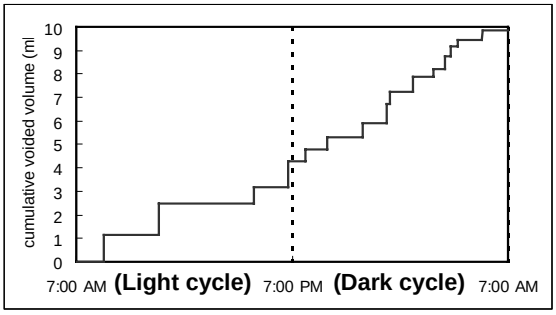
day	1st day	2nd day	3rd day	4th day	5th day	6th day
treatment	baseline	baseline	at 7a.m. 1ml of water	at 7a.m. ZP(2mg/Kg)/1ml	no drug, no vehicle	at 7 p.m. ZP(2mg/Kg)/1ml

Results

The initial baseline micturition studies showed a distinctive difference of micturition patterns between light and dark periods in both male and female rats. Rats, as a nocturnal animal, voided less frequently with larger volume during the daytime when they were sleeping than they did during the nighttime when they were awake (Fig.1, Table 1). ZP administration at the beginning of sleeping hours (7 a.m.) produced a significant increase in maximun voided volume during the light cycle in males(135.2±8.4%) and females(136.5±11.2%) when compared to the baseline data(Table2). However, all other micturition parameters(number of voids, mean V.V., maximun V.V. during dark cycle and urine production) were unchanged(Table 2). ZP administration at the beginning of waking hours (7 p.m.) on the last day did not significantly affect the micturition profile during both light and dark cycles in male and female rats when compared to the baseline profile.

Conclusions

The present study clearly demonstrates that micturition profile of rat also exhibits distinctive circadian rhythmicity whose frequency decreases during sleeping hours and increases during waking hours, and volume voided changes reciprocally. And this rhythmicity synchronizes well with L/D cycles. Thus, it can be stated that the micturition parameters are also chronobiologically regulated like other physiological variables. From the finding that the mean voided volume was increased during sleeping hours and the hypnotic agent enhanced the maximum voided volume only during sleeping hours, it is speculated that bladder capacity may be coupled with the depth of sleep. In fact, previous studies using EEG have reported that zolpidem increases slow wave sleep and results in an increase in NREM sleep and an increase in total sleep in rat[1)]. The implication of this study is that the chronological aspect of micturitoin should be considered when we study nocturia.



References

	male (n=8)		female (n=8)	
Body weight (g)	477.2±14.5		302.5±11.8	
actual water consumption (ml) (corrected for body weight (ml/Kg))	18.88±4.83 (33.44±8.57)		19.38±1.48 (59.27±4.51)	
	Light cycle	**Dark cycle**	**Light cycle**	**Dark cycle**
number of voids	4.22±0.91	11.51±4.59*	5.14±1.23	12.24±4.97**
mean voided volume(ml)	1.42±0.25	0.92±0.26*	1.08±0.34	0.73±0.28**
maximum voided volume(ml)	1.92±0.15	1.53±0.13	1.61±0.21	1.39±0.25
urine production(ml)	5.56±1.14	8.56±2.91*	5.53±3.54	7.37±2.87**

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Figure1. Graphical representation of a typical 24 hour micturition study from a metabolic cage experiment on a conscious rat.

Table1. Micturition Parameters in Baseline Study

mean ± SEM. *, ** ; p<0.05 significantly different from light cycle.

Table 2. The effects of ZP administered at the beginning of light period

		No.of voids		mean V.V.(ml)		maximum V.V.(ml)		urine production(ml)	
		L	D	L	D	L	D	L	D
male	Baseline	4.22 (0.91)	11.51 (4.59)	1.42 (0.25)	0.92 (0.26)	1.92 (0.15)	1.53 (0.13)	5.56 (1.14)	8.56 (2.91)
	ZP(7a.m.)	4.40 (0.45)	10.89 (3.98)	1.42 (0.65)	1.11 (0.33)	**2.60*** **(1.23)**	1.64 (0.23)	5.83 (2.26)	9.01 (2.83)
female	Baseline	5.14 (1.23)	12.24 4.97	1.08 (0.34)	0.73 (0.28)	1.61 (0.21)	1.39 (0.25)	5.53 (3.54)	7.37 (2.87)
	ZP(7a.m.)	5.04 (1.18)	12.87 (3.84)	1.12 (0.44)	0.83 (0.45)	**2.20**** **(0.43)**	1.32 (0.34)	5.21 (2.66)	8.54 (3.12)

mean (SEM). *, ** ; p<0.05 significantly different from baseline study.