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Rapid Increase to Double Breathing Rate Appears During REM Sleep in Synchrony with REM *–A Higher CNS Control of Breathing? –*

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Abstract Breathing rate (BR) during rapid eye movement (REM) sleep is known to fluctuate largely, while increases in BR during REM sleep reported were small. In our mice experiments, we found that mice exhibit a rapid increase in instantaneous BR (RIBR) of >2 fold during natural sleep with accompanying atonia, laying their sides down. The RIBR was further found in a sleeping mouse attached with EEG electrodes when the EEG amplitude and delta wave power were lower. Therefore, it is likely that mice show RIBRs during REM sleep. Interestingly, similar RIBRs accompanied by atonia and REM burst during REM sleep were also found in humans by standard polysomnographic studies in 11 healthy volunteers (age: 22.3 ± 2.8) with BR measurement by nasal/oral airflow sensors and chest/abdomen belt sensors. All subjects underwent RIBR of doubled BR at least once a night. As SpO_2 before RIBRs was a level not effective to be a respiratory stimulant (96.7 ± 1.6 %, $n = 63$), the RIBR seems to be controlled by higher central nervous system rather than autonomic nervous system control on response to central and peripheral chemical sensors. In fact, tachypnea with suppressed amplitude during RIBR resulted in a slight fall in SpO_2 (96.4 ± 1.7 %, $p = 0.0007$). In the present study, RIBRs accompanied by atonia and REM were not necessarily consistent in change in rate and/or amplitude, therefore, these various pattern of RIBRs may be potential indices of dreams with various emotional contents. Analysis of instantaneous BR, thus, may be a helpful tool for understanding the neural control of breathing during REM sleep.

1 Background and Purpose

It is widely accepted that breathing rate (BR) during rapid eye movement (REM) sleep fluctuates largely (Snyder et al. 1964), however, increase in BR during REM sleep reported was small, e.g., 9% in human (Aserinsky 1965) or 11% in mice (Friedman et al. 2004). In our experiments, we found that mice exhibit a rapid increase in instantanous BR (RIBR) of >2 fold during natural sleep with accompanying atonia, changing prone position to side down on a PZT sensor (Fig. 1). The PZT sensor (Sato et al. 2006) enabled noninvasive recording of RIBRs of freely moving mice during natural sleep without attaching any electrodes to their bodies (Sato et al. 2007). Following this, we assessed if RIBRs of doubled BR appear during REM sleep in humans similarly.

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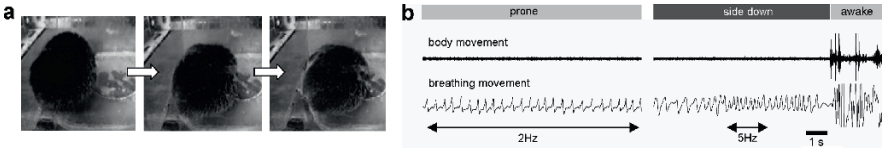

Fig. 1 Posture change observed in mice during natural sleep (**a**) and PZT signal indicating RIBR (**b**)

2 Methods

Mice experiments were performed by monitoring behavior during sleep with an infrared movie camera (MK-0323E; Akizuki, Japan) and respiratory activity with the PZT sensor system (ATC-402, Unique Medical, Japan; Sato, Yamada and Inagaki patent pending: PCT/JP2005/016520), which has good performance for noninvasive cardiorespiratory monitoring in mice (Sato 2008). A freely moving mouse was simply put on the PZT sensor that was placed in a transparent plastic box (Fig. 1a) and the PZT-sensor signal was high-pass and low-pass filtered for monitoring body and breathing movement, respectively (Fig. 1b). In human study, standard (10–20 system) polysomnographic recording was performed in 11 healthy volunteers (age: 22.3 ± 2.8, sex: male) with BR measurement by nasal/oral airflow sensors and chest/abdomen belt sensors. Sleep stage was scored utilizing the Rechtschaffen and Kales criteria. Instantaneous BR was calculated from intervals of respiratory signal peaks, which were obtained from the airflow-sensor signal by the peak detection analysis of signal analysis software, Clampfit 9.2 (Molecular Devices).

3 Results and Discussion

RIBRs appeared during atonia in mice, that is, presumably during REM sleep (Fig. 1). RIBRs were also found in mice attached with EEG electrodes during a period of low amplitude EEG, i.e., during REM sleep (Sato et al. 2009) consistent with urethane-anesthetized mice experiment (Clement et al. 2008). In human study, all subjects underwent RIBR, which increased to double the preceded BR or BR at deep sleep, at least once to several times during a night (Table 1). An example time course of instantaneous BR during sleep is shown in Fig. 2a and precise RIBR observations are in Fig. 2b–j. 90% of RIBRs were accompanied by REM and atonia; RIBRs appeared at onsets (b–d; see vertical bars) or at certain peaks in REM bursts (e–j). The amplitude of respiration signals during the RIBRs mostly decreased and the amount of change in BR and duration of tachypnea varied depending on individual REM bursts. The time for BR transition during RIBR was 4.3 ± 3.1 s (n = 63), within a couple of breaths.

In the present study, we demonstrated that humans and mice exhibit RIBRs of doubled (or more than doubled) BR during REM sleep with accompanying REM and atonia, which might be a heritable trait among mammals. During human REM sleep,

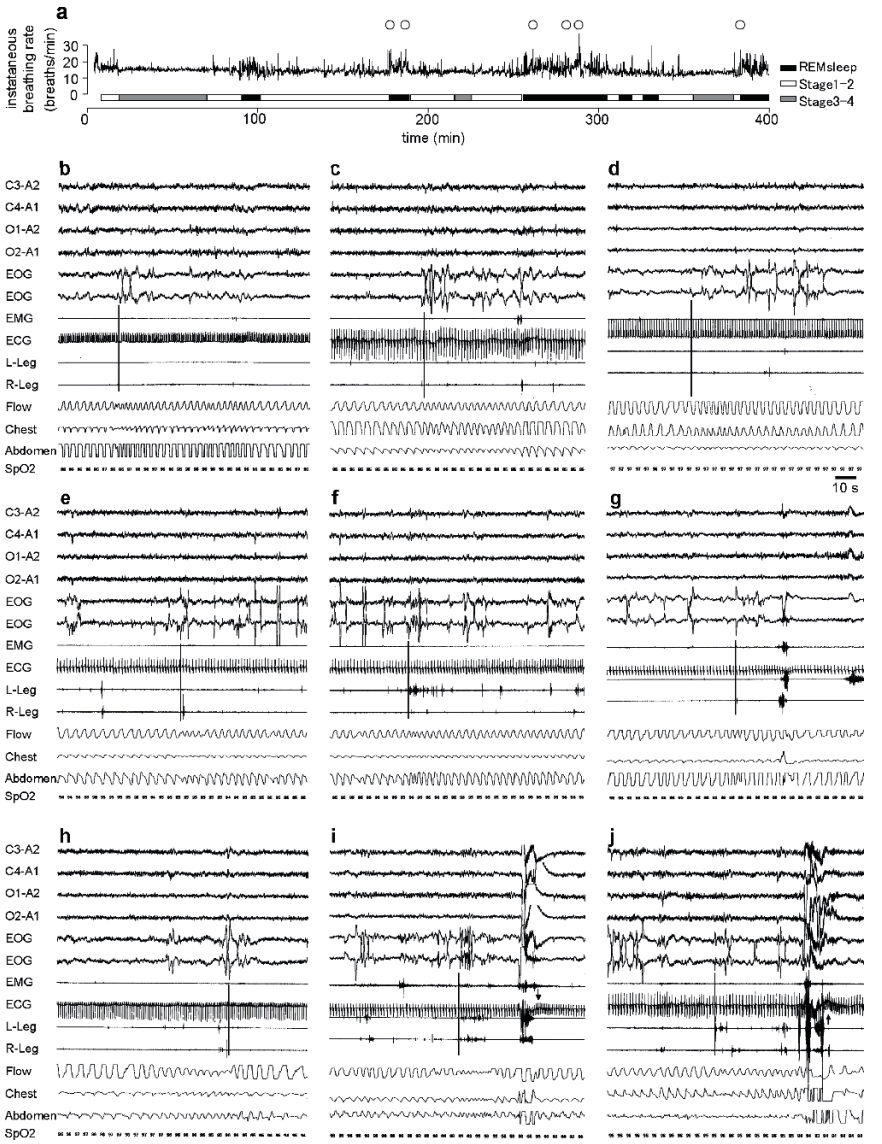

Fig. 2 A time course of instantaneous BR during sleep in a subject with several RIBRs (a:circles; some other large deflections are motion artifacts) and precise observations of RIBR associated with REM and atonia during REM sleep in several healthy young volunteers (**b**–**j**)

SpO_2 before RIBR was (96.7 ± 1.6 %, $n = 63$) a level not effective to be a respiratory stimulant; and tachypnea with suppressed amplitude during RIBR resulted in a slight fall in SpO_2 (96.4 ± 1.7 %, $p = 0.0007$). Decreased respiratory-response sensitivity to

Table 1 Number of REM sleep, RIBR and RIBR with REM observed during sleep in 11 subjects

ID	Number of REM sleep	Number of RIBR	Number of RIBR with REM
1	2	2	1
2	6	6	6
3	5	13	10
4	5	1	1
5	3	5	5
6	3	4	4
7	3	2	2
8	3	11	11
9	3	6	6
10	4	2	2
11	5	10	7

hypercapnic/hypoxic stimulus during REM sleep further reinforces that RIBRs are not likely to be mediated by autonomic response to hypercapnia/hypoxia. On the other hand, heart rate surges were not associated with REM nor RIBRs but it appeared with body movement (arrows; Fig. 2i–j) unlike an early study in cat (Rowe et al. 1999).

These results suggest that, during REM sleep, RIBR is mediated by a direct spinal-motor-neuron control or a respiratory-rhythm-generator control by a higher central nervous system activity. As RIBRs of doubled BR accompanied by REM and atonia were not necessarily consistent in change in rate and/or amplitude as depicted in an earlier study (Aserinsky 1965), various RIBR patterns may reflect dreams with various emotional contents. Thus, instantaneous BR analysis should be important to understand the mechanisms of the peculiar breathing activity during REM sleep.

References

Aserinsky, E. (1965) Periodic respiratory pattern occurring in conjunction with eye movements during sleep. Science 150(697), 763–766.

Clement, E.A., Richard, A., Thwaites, M., Ailon, J., Peters, S., and Dickson. C.T. (2008) Cyclic and sleep-like spontaneous alternations of brain state under urethane anaesthesia. PLoS ONE 3(4).

Friedman, L., Haines, A., Klann, K., Gallaugher, L., Salibra, L., Han, F., and Strohl, K.P. (2004) Ventilatory behavior during sleep among A/J and C57BL/6J mouse strains. J Appl. Physiol. 97(5),1787–1795.

Rowe, K., Moreno, R., Lau, T.R., Wallooppillai, U., Nearing, B.D., Kocsis, B., Quattrochi, J., Hobson, J.A, and Verrier, R.L. (1999) Heart rate surges during REM sleep are associated with theta rhythm and PGO activity in cats. Am. J Physiol. 277(3 Pt 2), R843–849.

Sato, S., Yamada, K., and Inagaki, N. (2006) System for simultaneously monitoring heart and breathing rate in mice using a piezoelectric transducer. Med. Biol. Eng. Comput. 44, 353–362.

Sato, S, Kanbayashi, T, Kondo, H, Matsubuchi, N., and Shimizu, T. (2007) Short period tachypnea during REM sleep in humans and mice. SLEEP 30, A34.

Sato, S. (2008) Quantitative evaluation of ontogenetic change in heart rate and its autonomic regulation in newborn mice with the use of a noninvasive piezoelectric sensor. Am. J Physiol. Heart Circ. Physiol. 294, H1708–H1715.

Sato, S., Kanbayashi, T., Kondo, H., Tokunaga, J., Sagawa, Y., Sato, M., Hosokawa, K., Ono, K., Inagaki, N., and Shimizu, T. (2009) Sleep-wake-like periodic change in EEG pattern accompanied by sudden increase in breathing rate in urethane anesthetized mice. SLEEP 32, A29.

Snyder, F., Hobson, J.A., Morrison, D.F., and Goldfrank F. (1964) Changes in respiration, heart rate, and systolic blood pressure in human sleep. J. Appl. Physiol. 19, 417–422.