

Conducted experiments: Zhang, Yan, Luo.

Performed data analysis: Zhang, Yan, Luo.

Wrote or contributed to the writing of the manuscript: Zhang, Yan, Rao.

References

- Alenina N, Kikic D, Todiras M, Mosienko V, Qadri F, Plehm R, Boyé P, Vilianovitch L, Sohr R, Tenner K, et al. (2009) Growth retardation and altered autonomic control in mice lacking brain serotonin. *Proc Natl Acad Sci USA* **106**:10332–10337.
- Berner NJ, Grahn DA, and Heller HC (1999) 8-OH-DPAT-sensitive neurons in the nucleus raphe magnus modulate thermoregulatory output in rats. *Brain Res* **831**:155–164.
- Boutrel B, Franc B, Hen R, Hamon M, and Adrien J (1999) Key role of 5-HT1B receptors in the regulation of paradoxical sleep as evidenced in 5-HT1B knock-out mice. *J Neurosci* **19**:3204–3212.
- Boutrel B, Monaca C, Hen R, Hamon M, and Adrien J (2002) Involvement of 5-HT1A receptors in homeostatic and stress-induced adaptive regulations of paradoxical sleep: studies in 5-HT1A knock-out mice. *J Neurosci* **22**:4686–4692.
- Buchanan GF and Richerson GB (2010) Central serotonin neurons are required for arousal to CO₂. *Proc Natl Acad Sci USA* **107**:16354–16359.
- Frank MG, Stryker MP, and Tecott LH (2002) Sleep and sleep homeostasis in mice lacking the 5-HT_{2c} receptor. *Neuropsychopharmacology* **27**:869–873.
- Hedlund PB, Huitron-Resendiz S, Henriksen SJ, and Sutcliffe JG (2005) 5-HT₇ receptor inhibition and inactivation induce antidepressant-like behavior and sleep pattern. *Biol Psychiatry* **58**:831–837.
- Hioki H, Nakamura H, Ma YF, Konno M, Hayakawa T, Nakamura KC, Fujiyama F, and Kaneko T (2010) Vesicular glutamate transporter 3-expressing non-serotonergic projection neurons constitute a subregion in the rat midbrain raphe nuclei. *J Comp Neurol* **518**:668–686.
- Hodges MR, Tattersall GJ, Harris MB, McEvoy SD, Richerson DN, Deneris ES, Johnson RL, Chen Z-F, and Richerson GB (2008) Defects in breathing and thermoregulation in mice with near-complete absence of central serotonin neurons. *J Neurosci* **28**:2495–2505.
- Huang Z-L, Qu W-M, Eguchi N, Chen J-F, Schwarzschild MA, Fredholm BB, Urade Y, and Hayaishi O (2005) Adenosine A_{2A}, but not A₁, receptors mediate the arousal effect of caffeine. *Nat Neurosci* **8**:858–859.
- Jouvet M (1968) Insomnia and decrease of cerebral 5-hydroxytryptamine after destruction of the raphe system in the cat. *Adv Pharmacol* **6** (Pt B):265–279.
- Jouvet M (1969) Biogenic amines and the states of sleep. *Science* **163**:32–41.
- Jouvet M (1972) The role of monoamines and acetylcholine-containing neurons in the regulation of the sleep-waking cycle, in *Neurophysiology and Neurochemistry of Sleep and Wakefulness* pp. 166–307. Springer, Berlin.
- Jouvet M, Bobillier P, Pujol JF, and Renault J (1967) Suppression of sleep and decrease of cerebral serotonin caused by lesion of the raphe system in the cat. *C R Acad Sci Hebd Seances Acad Sci D* **264**:360–362.
- Kim JY, Kim A, Zhao ZQ, Liu XY, and Chen ZF (2014) Postnatal maintenance of the 5-HT_{1a}-Pet1 autoregulatory loop by serotonin in the raphe nuclei of the brainstem. *Mol Brain* **7**:48.
- Koella WP, Feldstein A, and Czizman JS (1968) The effect of para-chlorophenylalanine on the sleep of cats. *Electroencephalogr Clin Neurophysiol* **25**:481–490.
- Kohtoh S, Taguchi Y, Matsumoto N, Wada M, Huang ZL, and Urade Y (2008) Algorithm for sleep scoring in experimental animals based on fast Fourier transform power spectrum analysis of the electroencephalogram. *Sleep Biol Rhythms* **6**:163–171.
- Liu Y, Jiang Y, Si Y, Kim J-Y, Chen Z-F, and Rao Y (2011) Molecular regulation of sexual preference revealed by genetic studies of 5-HT in the brains of male mice. *Nature* **472**:95–99.
- Liu Z, Zhou J, Li Y, Hu F, Lu Y, Ma M, Feng Q, Zhang JE, Wang D, Zeng J, et al. (2014) Dorsal raphe neurons signal reward through 5-HT and glutamate. *Neuron* **81**:1360–1374.
- Lytic R, McCarley RW, and Hobson JA (1987) Serotonin neurons and sleep. I. Long term recordings of dorsal raphe discharge frequency and PGO waves. *Arch Ital Biol* **125**:317–343.
- Macchitelli FJ, Fischetti D, and Montanarelli N, Jr (1966) Changes in behavior and electrocortical activity in the monkey following administration of 5-hydroxytryptophan (5-HTP). *Psychopharmacology (Berl)* **9**:447–456.
- McGinty DJ and Harper RM (1976) Dorsal raphe neurons: depression of firing during sleep in cats. *Brain Res* **101**:569–575.
- Monti JM (2011) Serotonin control of sleep-wake behavior. *Sleep Med Rev* **15**:269–281.
- Mouret J, Bobillier P, and Jouvet M (1967) Effect of parachlorophenylalanine on sleep in rats. *C R Seances Soc Biol Fil* **161**:1600–1603.
- Mouret J, Bobillier P, and Jouvet M (1968) Insomnia following parachlorophenylalanine in the rat. *Eur J Pharmacol* **5**:17–22.
- Nakamura K, Matsumura K, Hübschle T, Nakamura Y, Hioki H, Fujiyama F, Boldogkői Z, König M, Thiel H-J, Gerstberger R, et al. (2004) Identification of sympathetic premotor neurons in medullary raphe regions mediating fever and other thermoregulatory functions. *J Neurosci* **24**:5370–5380.
- Pack AI, Galante RJ, Maislin G, Cater J, Metaxas D, Lu S, Zhang L, Von Smith R, Kay T, Lian J, et al. (2007) Novel method for high-throughput phenotyping of sleep in mice. *Physiol Genomics* **28**:232–238.
- Paxinos G and Franklin KBJ (2008) *The Mouse Brain in Stereotaxic Coordinates, Compact, The Coronal Plates and Diagrams*, 3rd ed, Elsevier Academic Press, San Diego, CA.
- Popa D, Léna C, Fabre V, Prenat C, Gingrich J, Escourrou P, Hamon M, and Adrien J (2005) Contribution of 5-HT₂ receptor subtypes to sleep-wakefulness and respiratory control, and functional adaptations in knock-out mice lacking 5-HT_{2A} receptors. *J Neurosci* **25**:11231–11238.
- Portas CM and McCarley RW (1994) Behavioral state-related changes of extracellular serotonin concentration in the dorsal raphe nucleus: a microdialysis study in the freely moving cat. *Brain Res* **648**:306–312.
- Portas CM, Thakkar M, Rainnie D, and McCarley RW (1996) Microdialysis perfusion of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) in the dorsal raphe nucleus decreases serotonin release and increases rapid eye movement sleep in the freely moving cat. *J Neurosci* **16**:2820–2828.
- Pujol J-F, Buguet A, Froment J-L, Jones B, and Jouvet M (1971) The central metabolism of serotonin in the cat during insomnia. A neurophysiological and biochemical study after administration of P-chlorophenylalanine or destruction of the Raphé system. *Brain Res* **29**:195–212.
- Qu W-M, Xu X-H, Yan M-M, Wang Y-Q, Urade Y, and Huang Z-L (2010) Essential role of dopamine D₂ receptor in the maintenance of wakefulness, but not in homeostatic regulation of sleep, in mice. *J Neurosci* **30**:4382–4389.
- Sakai K and Crochet S (2001) Differentiation of presumed serotonergic dorsal raphe neurons in relation to behavior and wake-sleep states. *Neuroscience* **104**:1141–1155.
- Sos KE, Mayer MI, Cserép C, Takács FS, Szőnyi A, Freund TF, and Nyiri G (2016) Cellular architecture and transmitter phenotypes of neurons of the mouse median raphe region. *Brain Struct Funct* **222**:287–299.
- Tanaka M, Nagashima K, McAllen RM, and Kanosue K (2002) Role of the medullary raphe in thermoregulatory vasomotor control in rats. *J Physiol* **540**:657–664.
- Trulson ME and Jacobs BL (1979) Raphe unit activity in freely moving cats: correlation with level of behavioral arousal. *Brain Res* **163**:135–150.
- Whitney MS, Shemery AM, Yaw AM, Donovan LJ, Glass JD, and Deneris ES (2016) Adult brain serotonin deficiency causes hyperactivity, circadian disruption, and elimination of siestas. *J Neurosci* **36**:9828–9842.
- Zhao ZQ, Scott M, Chiechio S, Wang JS, Renner KJ, Gereau RW, IV, Johnson RL, Deneris ES, and Chen ZF (2006) Lmx1b is required for maintenance of central serotonergic neurons and mice lacking central serotonergic system exhibit normal locomotor activity. *J Neurosci* **26**:12781–12788.

Address correspondence to: Dr. Yi Rao, Peking University, 5 Yiheyuan Rd., Beijing 100871, China. E-mail: yrao@pku.edu.cn