Pharmacology, Biochemistry and Behavior 94 (2009) 250–254

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Quinine, a selective gap junction blocker, decreases REM sleep in rats

Javier Franco-Pérez [a,b], Carlos Paz [a,*]

[a] Departamento de Neurofisiología, Instituto Nacional de Neurología y Neurocirugía Insurgentes Sur No. 3877, Col. La Fama, C.P. 14269, México, D.F., Mexico
[b] Programa de Doctorado en Ciencias Biológicas, Universidad Nacional Autónoma de México, Ciudad Universitaria, Coyoacán, C.P. 04510, México, D.F., Mexico

ARTICLE INFO

Article history:
Received 29 April 2009
Received in revised form 24 August 2009
Accepted 1 September 2009
Available online 11 September 2009

Keywords:
Quinine
Gap junctions
Connexins
REM sleep
Slow wave sleep
Wakefulness

ABSTRACT

Electrical synapses are formed by gap junctions that allow the direct communication between neurons, the intercellular transference of ions and small molecules as well as the electrical coupling of the cells. Electrical coupling in neurons is mediated by the gap junction protein connexin36. There are reports about the presence of electrical coupling in the sublaterodorsal nucleus and pedunculopontine nucleus, which have been implicated in the modulation of the rapid eye movement sleep. In the present study, rats were used to examine the possible changes on the sleep–wake states after intracerebroventricular administration of several doses of quinine, a selective blocker of gap junctions formed by connexin36. The results showed that quinine significantly increased the time spent in wakefulness and decreased the time spent in slow wave sleep along the 24 h of polygraphic recording. The three doses used of quinine caused a significant decrease of rapid eye movement sleep along the light phase; however, only one dose extended such effect until the darkness phase. The changes on sleep–wake states of the rat after the blockage of gap junctions formed by connexin36 suggest that electrical synapses could contribute to the regulation of sleep–wake states in concert with the well-known chemical neurotransmission.

1. Introduction

Electrical synapses are characterized by a close approximation area (2–4 nm) between the membranes of two neurons. In this approximation area, the cells communicate through gap junctions, which constitute transmembranal channels formed by proteins called connexins (Connors and Long, 2004). These channels provide pathways of intercellular communication through which ions and small molecules pass (Giaume and Venance, 1998; Goldberg et al., 1999; Niessen et al., 2000). Based on some studies, it has been assumed that gap junctions formed by connexin36 (Cx36) mediate the electrical coupling between neurons (Hormuzdi et al., 2001; Christie et al., 2005). Therefore, due to reciprocity, speed and simplicity, gap junction channels can contribute to sharpen neuronal activity by synchronizing large neuronal populations (for references see Hormuzdi et al., 2004; Bennett and Zukin, 2004). The blockade of gap junction communication can be carried out by a number of factors, which include intracellular alkalinization, transjunctional voltage and some compounds like long-chain alcohols, halothane, glycyrrhetinic acid derivates and oleamide and derivates (Gonzalez-Nieto et al., 2008; Johnston et al., 1980; Davidson et al., 1986; Boger et al., 1998). However, it has been demonstrated that quinine, an antimalarial drug, is capable to block specifically Cx36 gap junctions in a reversible and concentration-dependent manner, but it does not affect other gap junction types (Srinivas et al., 2001).

The normal patterns of sleep depend on the complex interaction of several neurotransmission systems located throughout the brain. Between the multiple neuronal populations related with sleep–wake states, the pedunculopontine nucleus (PPN) and sublaterodorsal nucleus (SLD), also called subcoeruleus area, have been implicated in the control of rapid eye movement sleep (REMs) (Lu et al., 2006). Recent evidence suggests the presence of electrical synapses in PPN and SLD. Electrophysiological recordings of PPN and SLD neurons revealed that some of these are electrically coupled and the molecular analysis showed gene expression and protein levels of Cx36 in the mesopontine tegmentum, specifically in the PPN and SLD (Garcia-Rill et al., 2007; Heister et al., 2007).

It has been proposed that the presence of electrical coupling in both SLD and PPN could be a novel mechanism of action for the regulation of the sleep–wake states. However, there are no studies that describe the effects of the blockage in vivo of electrical synapses on the sleep parameters of the rat. Therefore, the aim of this study was to determine the changes on the sleep–wake states of the rat after intracerebroventricular (icv) administration of quinine, a selective blocker of Cx36 gap junctions.

2. Materials and methods

Male Wistar rats (280–320 g) were used for this study. Animals were maintained under controlled conditions (12–h light: 12–h darkness)

* Corresponding author. Departamento de Neurofisiología, Instituto Nacional de Neurología y Neurocirugía M.V.S., Insurgentes Sur No. 3877, Col. La Fama, C.P. 14269 México D.F., Mexico. Tel.: +52 55 5606 38 22; fax: +52 55 5424 08 08.
E-mail address: paztres@servidor.unam.mx (C. Paz).

0091-3057/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2009.09.003

and had free access to food and water. All animals were treated with suitable measures to minimize pain or discomfort according to regulations specified by the Animal Care and Use Committee of the National Institute of Neurology and Neurosurgery M.V.S., and according to the standards of the National Institutes of Health of Mexico.

Quinine hydrochloride was obtained from Sigma. Quinine was dissolved in 5% (v/v) dimethylsulfoxide purchased from Sigma.

Animals were anesthetized with ketamine (Laboratorios Pisa) (100 mg/kg, intraperitoneal); afterwards, bipolar electrodes were implanted in the left sensorimotor cortex for the electroencephalographic recordings (EEG), in the neck musculature to record the electromyogram (EMG) and in the external edge of the frontal bone to record eye movements (EOG). The bipolar electrodes were made of stainless-steel Teflon-coated wires (A-M Systems Inc) (0.005 in. diameter) with uncoated tips. An electrode implanted with a screw (Small Parts Inc) in the skull was used as an indifferent source of reference. A stainless-steel guide cannula (Becton Dickinson) was stereotaxically positioned 1 mm above the right lateral ventricle (0.8 mm posterior to Bregma, 1.4 mm lateral to midline, 3.6 mm below the surface of the skull) (Paxinos and Watson, 1998) for drug administration. Next, electrodes and guide cannula were fixed to a rectangular plug which was secured to skull with dental acrylic (Arias). Skin cuts were sutured and gentamicin (Laboratorios Pisa) was applied in a single intramuscular injection (40 mg/kg) to prevent posterior infection.

Rats implanted with electrodes and guide cannulas were randomly divided in the following groups: control ($n=8$) administered with vehicle (dimethylsulfoxide, 5%), quinine 0.5 μM ($n=6$), quinine 1.0 μM ($n=6$) and quinine 2.0 μM ($n=6$). After a 7 day period of recovery, rats were connected to an amplifier (BioScience Vector PSG32) by means of flexible cables so that they could move freely in a soundproof recording cage (12 in.×9 in.×9 in.). The cages were equipped with free access to food and water and under controlled light–dark conditions (8:00–20:00 h light, 20:00–8:00 h dark). Rats were habituated 48 h to become familiar with these laboratory conditions. For the icv administration, quinine was dissolved in vehicle (dimethylsulfoxide, 5%) and a total volume of 5 μL was injected through an injection cannula (Sofic) 1 mm longer than the guide cannula. Animals were gently hand-restrained and quinine infusions were made using an injection cannula connected by polyethylene tube to a 25 μL Hamilton syringe, the infusion rate was 1 μL/min.

Polygraphic recordings and behavioral observation began immediately after the infusion of vehicle or quinine (8:00 h approximately) and continued during 24 h. The polygraphic recordings were observed on a computer monitor and stored in the hard drive of a computer provided with Harmonie software developed by Stellate System for subsequent analysis of the sleep–wake states. The recording cages contained a video camera for continuous observation of the rats' behavior. The video file was also saved in the computer to help in the posterior determination of the sleep–wake states. The different states of the sleep–wake cycle were blindly analyzed by two experimenters who did not know about the drug treatment. The used criteria were those described previously (Franco-Pérez et al., 2006). Briefly: wakefulness (W), characterized by EEG desynchronization and presence of accentuated EMG activity; slow wave sleep (SWS), characterized by slow waves with high voltage and decreased EMG activity and rapid eye movement sleep (REMs) characterized by EEG desynchronization with the presence of rapid eye movements in the EOG and loss of muscle tone. The variables analyzed after the determination of sleep–wake states were the following: total time spent in W, SWS and REMs, as well as REMs parameters like number and mean duration of REMs episodes and latency of REMs onset (time interval between infusion of quinine and appearance of first REMs episode). These variables were analyzed for both control and quinine groups.

For time course of the effects of quinine on W, SWS and REMs we used a two-way ANOVA followed by a Tukey's post hoc test with both groups and time points as factors between subjects. REMs parameters were compared with one-way ANOVA followed by a Tukey's post hoc test.

3. Results

The effects of icv administration of three different doses of quinine (0.5, 1 and 2 μM) on sleep–wake states were evaluated. There are controversial reports about the availability of quinine in the brain after systemic administrations. Quinine does not seem to cross the blood–brain barrier in humans (Silamut et al., 1985). However, it has been reported that quinine is able to cross the brain barrier with the help of a blood–brain barrier permeator (Mikov et al., 2004). For this reason, we attempted to eliminate the possibility that quinine could be acting on peripheral systems and avoid in this way nonspecific effects through icv administration of low concentrations. Quinine was infused in rats at the beginning of light period (infusion time 8:00 h) and polygraphic recordings were done during 24 h to determine the effects of quinine across sleep–wake cycle.

In order to determine the time course of the effects of quinine, the duration of W, SWS and REMs in 1 h blocks along 24 h was analyzed. It was observed that quinine (1 μM) increased the duration of W mainly in the first 6 h of light phase; however, the same effect appeared in some points of dark phase, $F\ (3, 22)=41.25$, $p<0.001$ (Fig. 1). SWS was only altered by 1 μM of quinine, the time course analysis showed a significant decrease at the beginning of light phase and until the sixth hour of recording; a decrease of SWS at the end of dark phase was even observed, $F\ (3, 22)=31.20$, $p<0.001$ (Fig. 2). The experimental groups administered with quinine 0.5 and 2 μM only showed a slight change in both W and SWS during 2 h after injection of quinine. The most prominent effect caused by quinine was observed on REMs because all evaluated doses caused a significant reduction of this sleep state. Namely, administration of quinine 0.5 μM reduced REMs during the first 7 h of polygraphic recording. Again, the major effect was observed after quinine 1 μM, which dramatically reduced the time spent in REMs mainly during the 12 h of the light phase. On the other hand, quinine 2 μM slightly decreased the time spent in REMs at the beginning of the light phase, $F\ (3, 22)=41.01$, $p<0.001$ (Fig. 3).

Some REMs parameters like latency, number and mean duration of REMs episodes were also analyzed. All doses of quinine significantly increased the latency of REMs onset, $F\ (3, 22)=62.56$, $p<0.001$, and reduced the number of REMs episodes observed along 24 h, $F\ (3, 22)=20.05$, $p<0.001$. The mean duration of REMs episodes only decreased by the administration of 1 μM of quinine, $F\ (3, 22)=10.93$, $p<0.001$ (Fig. 4).

4. Discussion

It has been described that quinine has pharmacological properties capable to affect neurological functions (Juszczak and Swiergiel, 2009). Recently, it was demonstrated that quinine possesses anticonvulsant effects because intraperitoneal doses between 40 and 60 mg/kg decreased the duration of seizures induced by pentylenetetrazole (Nassiri-Asl et al., 2009). Bostanci and Bagirici (2007) established that quinine 1 μM applied to brain ventricle, significantly decreased epileptic discharges induced by penicillin. Importantly, quinine can potentiate the anesthetic effects produced by sodium pentobarbital (Nassiri-Asl et al., 2009). A previous study showed that quinine can cause changes in amplitude and power spectra of hippocampal theta rhythm of the cat (Golebiewski et al., 2006). Theta rhythm can be observed specially on W and REMs; however, there are no studies which describe properly the effects of quinine on sleep–wake pattern of the rat.

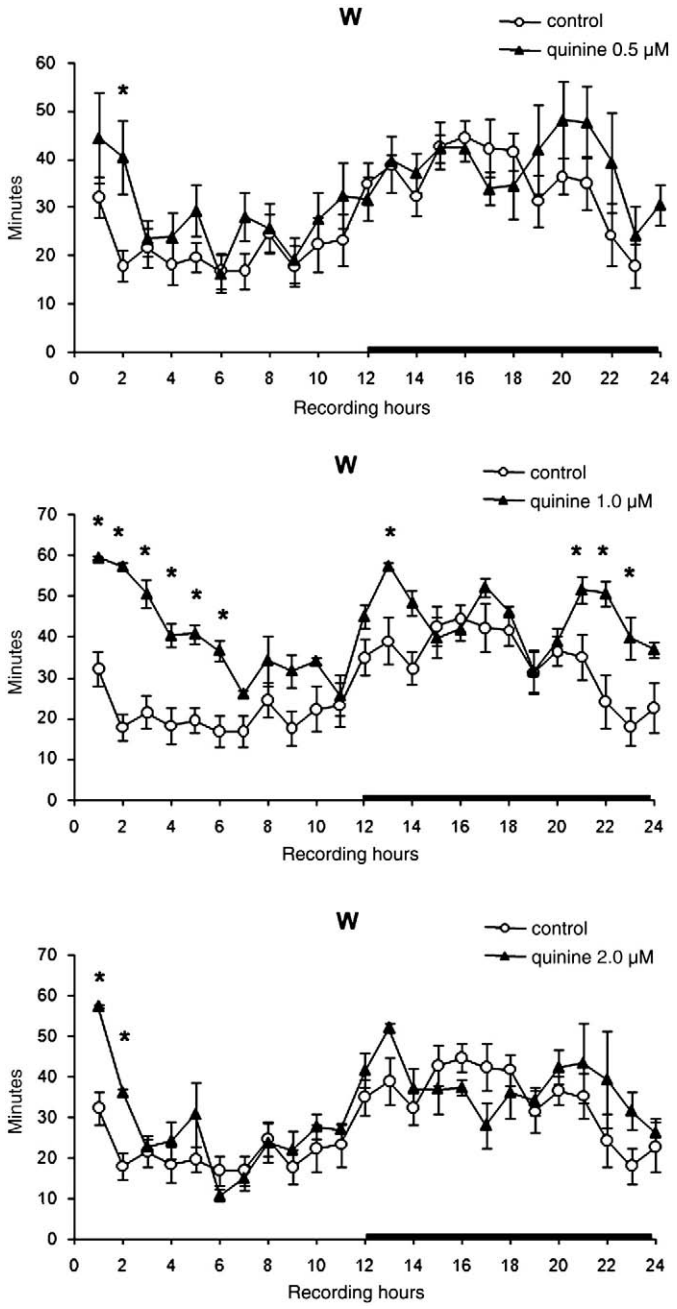

Fig. 1. Effects of icv administration of quinine on W in rats. The duration of W was evaluated hourly throughout one 12 h light:12 h darkness cycle. The results were compared statistically using a two-way ANOVA followed by a Tukey's test; $*p<0.001$. The horizontal black bars on the *X*-axis represent the dark phase of the cycle.

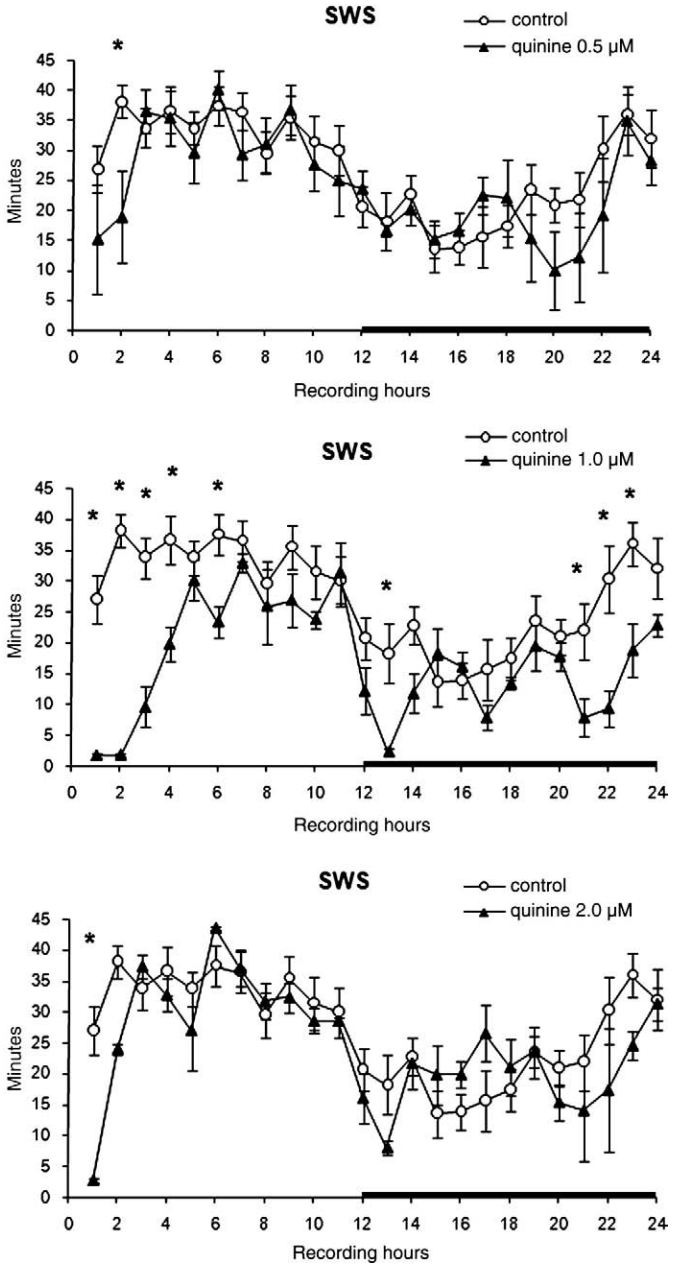

Fig. 2. Effects of icv administration of quinine on SWS in rats. The duration of SWS was evaluated hourly throughout one 12 h light:12 h darkness cycle. The results were compared statistically using a two-way ANOVA followed by a Tukey's test; $*p<0.001$. The horizontal black bars on the *X*-axis represent the dark phase of the cycle.

Some data suggest that quinine has indirect effects which could affect the sleep–wake pattern. It is known that intravenous quinine administration decreases the plasmatic glucose concentration and increases plasma insulin levels (Davis et al., 1993). It has been demonstrated that intraperitoneal administration of insulin is capable of decreasing the total time spent in REMs, probably due to changes in monoamine concentrations implicated in REMs regulation (Sangiah et al., 1982). On the other hand, it has been observed that quinine has the ability to block different types of potassium currents (Imai et al., 1999). Compounds which block potassium channels prolong depolarization and cause an increase on the release of neurotransmitter. Consequently, quinine is capable to increase the spontaneous release of glutamate from rat cerebellar slices (Barnes et al., 1989). Recently, it was described that bilateral microinjections of glutamate in the rat brain significantly increase the time spent in waking and concomitantly decrease the time spent in SWS and REMs (Alam and Mallick, 2008). Thus, although it is possible that quinine exerts its effects by preventing gap junction-mediated communication between neurons involved in REMs regulation; it is also possible that quinine causes changes on sleep–wake states by another indirect mechanism.

Quinine, a drug used for the treatment of malaria and benign nocturnal leg clamps, closes gap junction channels in a reversible, concentration-dependent and connexin-specific manner. It has been demonstrated that in vitro quinine selectively blocked Cx36 gap junctions and did not have an effect on gap junctions formed by other connexins (Srinivas et al., 2001). Further evidence of the possible involvement of gap junctions on the sleep–wake cycle is described in some reports which indicate that oleamide and anandamide have sleep-inducing properties because icv injection increases SWS and

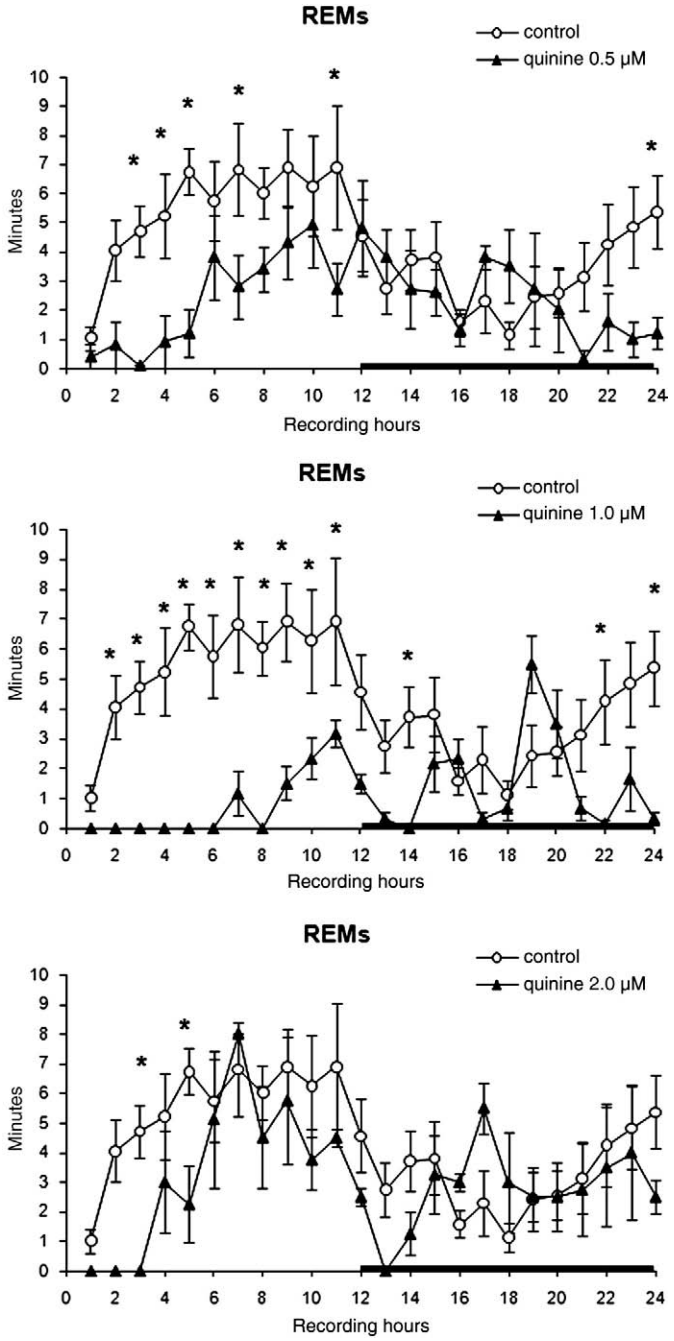

Fig. 3. Time course of the effects of quinine administration on REMs. The duration of REMs was evaluated every hour throughout one 12 h light:12 h darkness cycle. The results were compared statistically using a two-way ANOVA followed by a Tukey's test; $^{*}p < 0.001$. The horizontal black bars on the *X*-axis represent the dark phase of the cycle.

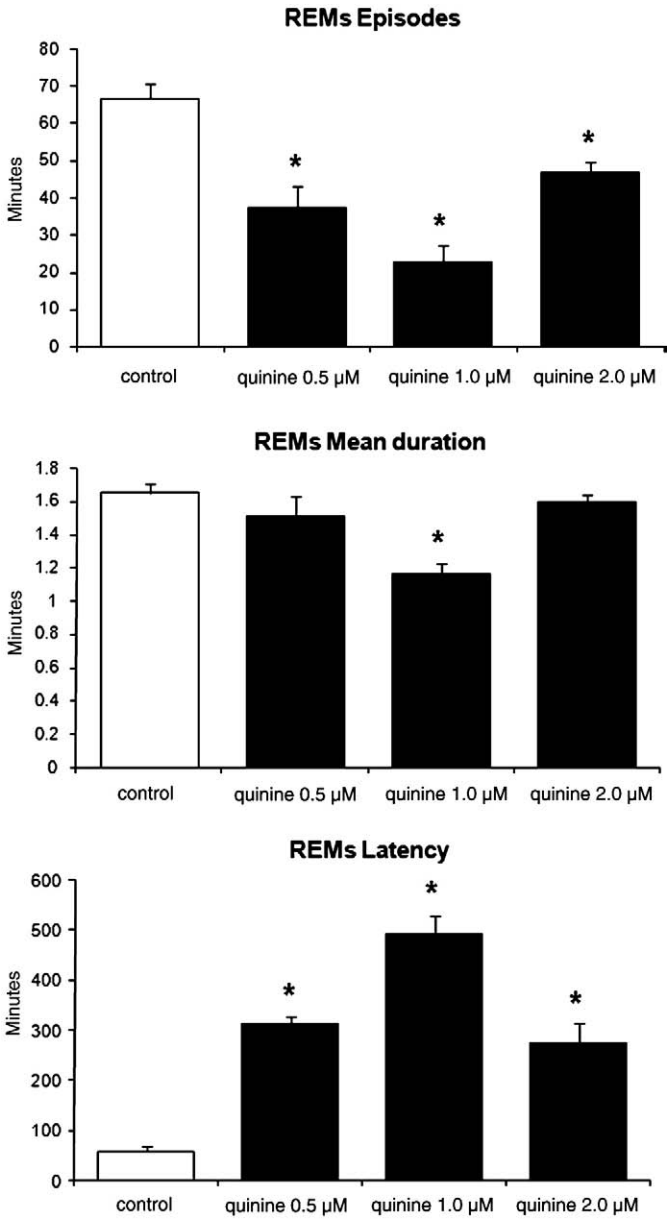

Fig. 4. REMs parameters after icv administration of quinine. Results are expressed as mean ± SEM of 6–8 animals per group. Statistical analysis was carried out by one-way ANOVA followed by a Tukey's test; $^{*}p < 0.001$.

REMs at the expense of W (Cravatt et al., 1995; Murillo-Rodríguez et al., 1998). Communication between glial cells is mediated by Cx43 gap junctions and can be blocked by oleamide, an endogenous fatty acid primary amide (Guan et al., 1997) and anandamide, an endogenous arachidonic acid derivative (Venance et al., 1995). So far, participation of gap junctions on sleep–wake states has not yet received enough attention since the research has been focused on chemical neurotransmission and sleep-inducing molecules.

Many neurons in the mammalian central nervous system communicate through electrical synapses which are constituted by membrane-to-membrane appositions called gap junctions (Connors and Long, 2004). Based on some studies, it has been assumed that Cx36 gap junctions mediate the electrical coupling between neurons (Hormuzdi et al., 2001; Christie et al., 2005). Recent data suggest that a significant proportion of SLD and PPN neurons are electrically coupled. Such assertion has been confirmed by electrophysiological recordings of neighboring PPN neurons suspended in a tetrodotoxin medium, in which hyperpolarizing pulses delivered to one cell induced a current in the other cell and vice versa; thus indicating that such neurons were electrically coupled (Garcia-Rill et al., 2007). We used quinine to block gap junction channels and thus lead a dysregulation of electrical coupling in brain regions containing Cx36 gap junctions, principally in neurons of the PPN. Our findings indicate that administration of quinine modifies the architecture of sleep mainly by altering the duration of REMs. Therefore, we can hypothesize that a dysregulation of electrical coupling could originate changes on the sleep–wake states in the rat. Molecular evidence indicates the presence of both Cx36 gene expression and protein in SLD nucleus, which were reduced during the developmental decrease of REMs (Heister et al., 2007). Among the multiple neuronal populations related with sleep–wake states, the PPN and SLD have

been implicated in the control of REMs (Lu et al., 2006). This hypothesis has been supported with reports which indicate that some PPN neurons show increased rates of firing during W and REMs, but such firing rate decreases during SWS (Steriade et al., 1990; Datta and Sywek, 2002). On the other hand, high levels of c-Fos expression in SLD after REMs enhancement have been demonstrated (Lu et al., 2006) and a previous study reported that disinhibition of SLD by bicuculline induced a REMs-like state (Boissard et al., 2002). Thus, it has been proposed that the presence of electrical coupling, mediated by Cx36 gap junctions, in both SLD and PPN could be a novel mechanism of action for the regulation of the sleep–wake states. In the present study, Cx36 gap junctions were specifically blocked by means of icv administration of quinine. According to our findings, quinine significantly decreased total time spent in REMs, which was mainly due to a reduction of REMs episodes. Therefore, results obtained in this study strongly suggest that modification in the activity of gap junctions, caused by the effect of quinine, could be involved in the reduction of the expression of REM sleep.

Modafinil is used for the treatment of narcolepsy, shift work sleep disorder and excessive daytime sleepiness associated with obstructive sleep apnea, because it has the capability to promote W in patients (Kumar, 2008). It has been described that modafinil modifies electrical coupling between neurons of some brain areas (Urbano et al., 2007; Garcia-Rill et al., 2007; Beck et al., 2008). Therefore, this suggests that modifications of electrical coupling in the regions related to modulation of sleep–wake states and enriched with Cx36 gap junctions, can promote changes on sleep–wake states. Nevertheless, mechanisms by which electrical coupling disruption can alter sleep–wake cycle are still not clear. The results shown in this paper provide additional information indicating that selective blockade of Cx36 gap junctions by quinine can modify the normal sleep pattern of the rat. Indeed, these findings support both the participation of Cx36 gap junctions in structures related to sleep regulation and the hypothesis that electrical coupling plays an important role in the modulation of sleep–wake states.

Finally, we can confirm that changes of sleep–wake states of the rat observed after icv administration of quinine are not due to vehicle used (dimethylsulfoxide), because it has been reported that 5% dimethylsulfoxide treatment did not have significant effects on sleep pattern of the rat (Cavas et al., 2005). In conclusion, the results of this study demonstrate that blockage of Cx36 gap junctions produces changes on the sleep–wake states in rats.

Acknowledgements

This study was supported by CONACyT-Mexico Grant 49920-Q to C.P. and the fellowship 49130 for J.F.P.'s Doctoral Dissertation in the Programa de Posgrado en Ciencias Biologicas of UNAM.

References

Alam MA, Mallick BN. Glutamic acid stimulation of the perifornical–lateral hypothalamic area promotes arousal and inhibits non-REM/REM sleep. Neurosci Lett 2008;439:281–6.
Barnes S, Whitham EM, Davies JA. Effects of potassium channel blockage on endogenous glutamate release from cerebellar slices. Brain Res 1989;486:89–94.
Beck P, Odle A, Wallace-Huitt T, Skinner RD, Garcia-Rill E. Modafinil increases arousal determined by P13 potential amplitude an effect blocked by gap junction antagonist. Sleep 2008;31:1647–54.
Bennett MV, Zukin RS. Electrical coupling and neuronal synchronization in the mammalian brain. Neuron 2004;41:495–511.
Boissard R, Gervasoni D, Schmidt MH, Barbagli B, Fort P, Luppi P. The rat ponto-medullary network responsible for paradoxical sleep onset and maintenance: a combined microinjection and functional neuroanatomical study. Eur J Neurosci 2002;16:1959–73.
Boger DL, Patterson JE, Guan X, Cravatt BF, Lerner RA, Gilula NB. Chemical requirements for inhibition of gap junction communication by the biologically active lipid oleamide. Proc Natl Acad Sci U S A 1998;95:4810–5.
Bostanci MO, Bagirici F. Anticonvulsive effects on penicillin-induced epileptiform activity: an *in vivo* study. Seizure 2007;16:166–72.
Cavas M, Beltrán D, Navarro JF. Behavioural effects of dimethyl sulfoxide (DMSO): changes in sleep architecture in rats. Toxicol Lett 2005;157:221–32.
Christie JM, Bark C, Hormuzdi SG, Helbig I, Monyer H, Westbrook GL. Connexin36 mediates spike synchrony in olfactory bulb glomeruli. Neuron 2005;46:761–72.
Connors BW, Long MA. Electrical synapses in the mammalian brain. Annu Rev Neurosci 2004;27:393–418.
Cravatt BF, Prospero-Garcia O, Siuzdak G, Gilula NB, Henriksen SJ, Boger DL, et al. Chemical characterization of a family of brain lipids that induce sleep. Science 1995;268:1506–9.
Datta S, Sywek DF. Single cell activity patterns of pedunculopontine tegmentum neurons across the sleep–wake cycle in the freely moving rats. J Neurosci Res 2002;70:611–21.
Davidson JS, Baumgarten IM, Harley EH. Reversible inhibition of intercellular junctional communication by glycyrrhetinic acid. Biochem Biophys Res Commun 1986;134:29–36.
Davis TM, Looareesuwan S, Pukrittayakamee S, Levy JC, Nagachinta B, White NJ. Glucose turnover in severe falciparum malaria. Metabolism 1993;42:334–40.
Franco-Pérez J, Padilla M, Paz C. Sleep and brain monoamine changes produced by acute and chronic acetaldehyde administration in rats. Behav Brain Res 2006;174:86–92.
Garcia-Rill E, Heister D, Ye M, Charlesworth A, Hayar A. Electrical coupling: novel mechanism for sleep–wake cycle. Sleep 2007;30:1403–12.
Giaume C, Venance L. Intercellular calcium signaling and gap juctional communication in astrocytes. Glia 1998;24:50–64.
Goldberg GS, Lampe PD, Nicholson BJ. Selective transfer of endogenous metabolites through gap junctions composed of different connexins. Nat Cell Biol 1999;1:457–9.
Golebiewski H, Eckersdorf B, Konopacki J. Electrical coupling underlies theta rhythm in freely moving cats. Eur J Neurosci 2006;24:1759–70.
Gonzalez-Nieto D, Gomez-Hernandez JM, Larrosa B, Gutierrez C, Muñoz MD, Fasciani I, et al. Regulation of neuronal connexin-36 channels by pH. Proc Natl Acad Sci U S A 2008;105: 17169–74.
Guan X, Cravatt BF, Ehring GR, Hall JE, Boger DL, Lerner RA, et al. The sleep-inducing lipid oleamide deconvolutes gap junction communication and calcium wave transmission in glial cells. J Cell Biol 1997;139:1785–92.
Heister D, Hayar A, Charlesworth A, Yates C, Zhou Y, Garcia-Rill E. Evidence for electrical coupling in the subcoeruleus (SubC) nucleus. J Neurophysiol 2007;97:3142–7.
Hormuzdi SG, Pais I, LeBeau F, Towers SK, Rozov A, Buhl EH, et al. Impaired electrical signaling disrupts gamma frequency oscillations in connexin 36-deficient mice. Neuron 2001;31:487–95.
Hormuzdi SG, Filippov MA, Mitropoulou G, Monyer H, Bruzzone R. Electrical synapses: a dynamic signaling system that shapes the activity of neuronal networks. Biochim Biophys Acta 2004;1662:113–37.
Imai S, Suzuki T, Sato K, Tokimasa T. Effects of quinine on three different types of potassium currents in bullfrog sympathetic neurons. Neurosci Lett 1999;275:121–4.
Johnston MF, Simon SA, Ramon F. Interaction of anesthetics with electrical synapses. Nature 1980;286:498–500.
Juszczak GR, Swiergiel AH. Properties of gap junction blockers and their behavioural, cognitive and electrophysiological effects: animal and human studies. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:181–98.
Kumar R. Approved and investigational uses of modafinil: an evidence-based review. Drugs 2008;68:1803–39.
Lu J, Sherman D, Devor M, Saper C. A putative flip-flop switch for control of REM sleep. Nature 2006;441:589–94.
Mikov M, Kevresan S, Kuhajda K, Jakovljevic V, Vasovic V. 3Alpha, 7alpha-dihydroxy-12-oxo-5beta-cholonate as blood–brain barrier permeator. Pol J Pharmacol 2004;56:367–71.
Murillo-Rodríguez E, Sánchez-Alavez M, Navarro L, Martínez-González D, Drucker-Colin R, Prospero-García O. Anandamide modulates sleep and memory in rats. Brain Res 1998;812:270–4.
Nassiri-Asl M, Zamansoltani F, Torabinejad B. Antiepileptic effects of quinine in the pentylenetetrazole model of seizure. Seizure 2009;18:129–32.
Niessen H, Hart H, Bedner P, Kramer K, Willecke K. Selective permeability of different connexin channels to the second messenger inositol 1, 4, 5-triphosphate. J Cell Sci 2000;113:1365–72.
Paxinos G, Watson A. The rat brain in stereotaxic coordinates. 4th ed. San Diego: Academic Press; 1998.
Sangiah S, Caldwell DF, Villeneuve MJ, Clancy JJ. Sleep: sequential reduction of paradoxical (REM) and elevation of slow wave (NREM) sleep by a non-convulsive dose of insulin in rats. Life Sci 1982;31:763–9.
Silamut K, White NJ, Looareesuwan S, Warrel DA. Binding of quinine to plasma proteins in falciparum malaria. Am J Trop Med Hyg 1985;34:681–6.
Srinivas M, Hopperstand MG, Spray DC. Quinine blocks specific gap junction channel subtypes. Proc Natl Acad Sci U S A 2001;98:10942–7.
Steriade M, Datta S, Pare D, Oakson G, Currodossi R. Neuronal activities in brain-stem cholinergic nuclei related to tonic activation process in thalamocortical systems. J Neurosci 1990;10:2541–59.
Urbano FJ, Leznik E, Llinás RR. Modafinil enhances thalamocortical activity by increasing neuronal electrotonic coupling. Proc Natl Acad Sci U S A 2007;104:12554–9.
Venance L, Piomelli D, Glowinski J, Giaume C. Inhibition by anandamide of gap junctions and intercellular calcium signaling in striatal astrocytes. Nature 1995;376: 590–4.