MEDICAL SCIENCE MONITOR

ANIMAL STUDY

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 542-549
DOI: 10.12659/MSM.893414

Received: 2014.12.26
Accepted: 2015.02.04
Published: 2015.02.19

Effects of Sleep Deprivation on Action Potential and Transient Outward Potassium Current in Ventricular Myocytes in Rats

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Source of support: This study was supported by the Special Project of the "Eleventh Five-year Plan" for Medical Science Development of PLA (Caiyi Lu 08G124)

Background: Sleep deprivation contributes to the development and recurrence of ventricular arrhythmias. However, the electrophysiological changes in ventricular myocytes in sleep deprivation are still unknown.

Material/Methods: Sleep deprivation was induced by modified multiple platform technique. Fifty rats were assigned to control and sleep deprivation 1, 3, 5, and 7 days groups, and single ventricular myocytes were enzymatically dissociated from rat hearts. Action potential duration (APD) and transient outward current (I_{to}) were recorded using whole-cell patch clamp technique.

Results: Compared with the control group, the phases of APD of ventricular myocytes in 3, 5, and 7 days groups were prolonged and APD at 20% and 50% level of repolarization (APD_{20} and APD_{50}) was significantly elongated (The APD_{20} values of control, 1, 3, 5, and 7 days groups: 5.66±0.16 ms, 5.77±0.20 ms, 8.28±0.30 ms, 11.56±0.32 ms, 13.24±0.56 ms. The APD_{50} values: 50.66±2.16 ms, 52.77±3.20 ms, 65.28±5.30 ms, 83.56±7.32 ms, 89.24±5.56 ms. $P<0.01$, $n=18$). The current densities of I_{to} significantly decreased. The current density-voltage (I–V) curve of I_{to} was vitally suppressed downward. The steady-state inactivation curve and steady-state activation curve of I_{to} were shifted to left and right, respectively, in sleep deprivation rats. The inactivation recovery time of I_{to} was markedly retarded and the time of closed-state inactivation was markedly accelerated in 3, 5, and 7 days groups.

Conclusions: APD of ventricular myocytes in sleep deprivation rats was significantly prolonged, which could be attributed to decreased activation and accelerated inactivation of I_{to}.

MeSH Keywords: Action Potentials • Patch-Clamp Techniques • Sleep Deprivation

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/893414

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Background

Sleep disorder is a growing problem in modern society that affects life quality and is becoming a major health problem [1]. Both acute and chronic sleep restriction have adverse effects on cardiovascular system, immune responses, hormonal pathways, and thermoregulation. Human studies show that sleep deprivation can increase activation of the autonomic nervous system (ANS), the hypothalamic-pituitary-adrenal axis, and the immune system [2–6]. Sgoifo et al. reported that the heart rate and hypothalamic-pituitary-adrenocortical (HPA) axis activity significantly increased after 48-h sleep deprivation [1]. Some studies reported that electrocardiographic changes result from parasympathetic and sympathetic tones imbalance caused by sleep deprivation. Both in healthy young adults and in rat models, it had been documented that acute sleep deprivation was associated with the increase of QT interval and QT dispersion, which suggests that sleep deprivation may increase the risk of ventricular arrhythmia [7,8]. It had been known that the prolongation of the action potential duration (APD) can result in the increase of the QT interval and QT dispersion. Change of transient outward current (I_{to}) is an important ionic mechanism that contributes to this process in several pathophysiologic conditions [9,10]. However, little is known about the effects of sleep deprivation on the ion channels, such as I_{to} of ventricular myocytes. The present study was designed to investigate the effects of sleep deprivation on the APD and I_{to} of rat ventricular myocytes.

Material and Methods

Animals

Fifty Sprague-Dawley adult male rats (200–250 g) were housed in cages with a 12-h: 12-h light-dark cycle, and the room temperature was controlled at 22–24°C. Before sleep deprivation, rats were allowed to stay in the same cage for 2 weeks to establish a social hierarchy within the group. All procedures of this study complied with the Guide for the Care and Use of Laboratory Animals. The rats were provided by Beijing Vital River Laboratory Animal Technology Co. Ltd. and the certificate no. was SCXK (Jing) 2012-0009.

Experimental procedure

The same tank used for the sleep deprivation group was used for the platform control group, but a platform (30.0×18.0 cm) was placed in cage, and rats had certain activities and could sleep on the platform. For the SD groups, rats were divided into groups based on the duration of SD: 1, 3, 5, and 7 days (10 rats for each duration). Methods for sleep deprivation were that rats were group-housed (5 rats in each arena) in modified multiple platform arenas during SD. The experimental group was submitted to SD using the modified multiple platform method. Briefly, rats were placed in an acrylic water tank (70×50×40 cm) containing 5 circular platforms, 6.3 cm in diameter, with water filled to 1 cm beneath the surface of platforms. The rats could move around inside the tank by jumping from 1 platform to another. This method relies on the muscle atonia that accompanies paradoxical sleep. When the rats on the platforms reach this sleep stage, they lose muscle tone; therefore, they either touch or fall into the surrounding water, so they are awakened. The modified multiple platform method completely abolishes paradoxical sleep and also decreases slow wave sleep by approximately 35% [11]. Food and water were provided by placing food pellets and water bottles on a grid located on top of the tank. The water in the tank was changed daily throughout the SD period.

Solutions [12]

Tyrode's solution contained (mM/L): NaCl 126, KCl 5.4, $MgCl_2$ 1, $CaCl_2$ 1.8, NaH_2PO_4 0.33, glucose 10 and 4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) 10, pH adjusted to 7.4 with NaOH. The Ca^{2+}-free Tyrode's solution was prepared by removing $CaCl_2$ from the Tyrode's solution.

The enzyme solution used for the rat cardiomyocyte isolation contained 0.1g/L collagenase (type II) and 0.5g/L BSA in Tyrode's solution.

For recording I_{to} currents, the pipettes were filled with (mM/L): K-aspartame acid 140, MgATP 4, $MgCl_2$ 1, Ethylene glycol tetraacetic acid (EGTA) 10, Guanosine triphosphate (GTP) 0.1, HEPES 10, pH adjusted to 7.3 with KOH.

For recording I_{to} currents, myocytes were superfused with solution containing (mM/L): NaCl 140, KCl 4, $CaCl_2$ 1, $MgCl_2$ 1, HEPES 10, glucose 5, pH adjusted to 7.4 with NaOH. Tetrodotoxin inhibits Na^+ current; $CdCl_2$ inhibits Ca^{2+} current.

Cell preparations

After SD, rats were given intraperitoneal injection of pentobarbital sodium (100 mg/kg) and a single ventricular myocyte was dissociated from excised perfused hearts by an enzymatic dissociation as previously described [12]. Briefly, hearts were excised rapidly and retrogradely perfused on a Langendorff apparatus with a Ca^{2+}-free Tyrode's solution for 5 min before the perfusate was switched to an enzymatic solution for 15 min. The perfusates were bubbled with 95% O_2 +5% CO_2 and maintained at 37°C. The ventricles were cut into small chunks and gently agitated in Ca^{2+}-free Tyrode's solution. The cells were filtered through nylon mesh (pore size 200 μm) and stored in Ca^{2+}-free Tyrode's solution at 4°C.

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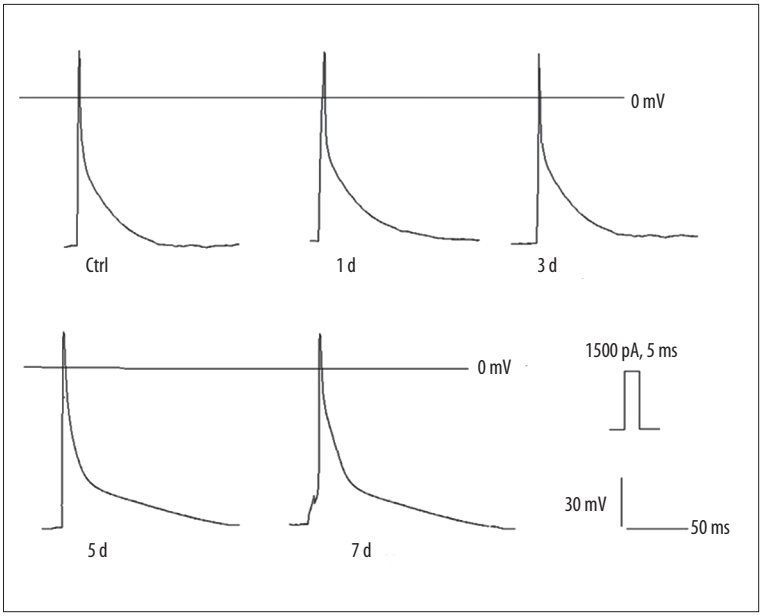

Figure 1. The action potential traces in different sleep deprivation groups. Action potential traces were recorded in sleep deprivation 1, 3, 5, and 7 days groups and the control group. The APDs were prolonged after 3, 5, and 7 days of sleep deprivation compared with control group. Ctrl: control group.

Electrophysiological measurements

Patch clamp experiments were performed on isolated ventricular cardiomyocytes. Quiescent, calcium-tolerant, rod-shaped cells with clear cross striation were used for action potential recordings at 35°C. Transmembrane potentials and currents were recorded using the whole cell patch-clamp technique with a MultiClamp 700B amplifier (Axon Instruments). All signals were acquired at 5 kHz (Digidata 1322A, Axon Instruments) and analyzed by pCLAMP version 9.2 software (Axon Instruments). Whole-cell currents and Action potentials (APs), obtained under voltage clamp, were filtered at 1–5 kHz and sampled at 5–50 kHz, and the series resistance was typically <5 mega ohms after about 70% compensation. The P/4 protocol was used to subtract online the leak and capacitive transients.

APs were elicited using the current-clamp mode at a rate of 5.0 Hz of 30 train suprathreshold current pulses. Cardiomyocytes were electrically stimulated by intracellular current injection through patch electrodes using depolarizing pulses with a duration of 5 ms and an amplitude of 1500 pA. Action potential duration (APD) was measured at 20% and 50% of repolarization (APD_{20} and APD_{50}). I_{to} was recorded using the voltage-clamp mode. We used pre-pulse to –40 mV for 30 ms to inactivate I_{Na}. I_{to} was recorded in voltage-clamp mode with 300-ms pulses from a holding potential of –80 mV, with different test potentials increased from –40 mV to +70 mV with 10-mV steps. Steady-state activation of I_{to} was induced by voltage steps between –60 mV and +40 mV for 500 ms from a holding potential of –80 mV.

Steady-state inactivation of I_{to} was induced by a condition pulse of +40 mV for 20 ms, following voltage steps between –120 mV to +30 mV, with 10 mV for 1000 ms. Voltage-dependence of the time course of recovery from inactivation was evaluated with a paired-pulse protocol: conditioning pulse was applied to +40 mV for 300 ms from holding potential of –80 mV, following test potentials of +40 mV for 300 ms during different time intervals of 20 ms,40 ms,80 ms, 160 ms, 320 ms, 640 ms, and 920 ms. The time course of recovery from fast inactivation was fitted by single-exponential function. The time constant of closed-state inactivation of I_{to} was induced by following depolarization pulse of +50mV for 300 ms return to –100 mV, depolarizing to –70 mV during different time pluses of 10 ms, 20 ms, 50 ms, 100 ms, 200 ms, 500 ms, 1000 ms, 2000 ms, 2500 ms, 4000 ms and 5000 ms. Time constant of inactivation was fitted by single-exponential function.

Statistical analysis

The data are presented as Mean ±SD. The curves were fitted with pCLAMP 10.0 (Axon Instruments) and software Origin 6.0. The statistical significance was determined using ANOVA to compare multiple groups. A value of $P<0.05$ was considered statistically significant.

Results

Effects of sleep deprivation on APD

Action potential traces were recorded in sleep deprivation 1, 3, 5, and 7 days groups and compared with the control group. Figure 1 showed that the action potential duration was prolonged after 3 days of sleep deprivation. The APD_{20} values of the 3, 5, and 7 days SD groups (8.28±0.30 ms, 11.56±0.32 ms

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Table 1. 20% of action potential duration (APD_{20}) and 50% of action potential duration (APD_{50}) in sleep deprivation and control groups.

Groups	APD_{20} (ms)	APD_{50} (ms)
Control	5.66±0.16	50.66±2.16
1d	5.77±0.20	52.77±3.20
3d	8.28±0.30*	65.28±5.30*
5d	11.56±0.32*	83.56±7.32*
7d	13.24±0.56*	89.24±5.56*

APD_{20} and APD_{50} were markedly prolonged in the 3, 5, and 7 days SD groups. * P<0.01 *vs.* Control (n=18). APD_{20}, APD_{50}: action potential duration measured at 20% and 50% of repolarization, respectively.

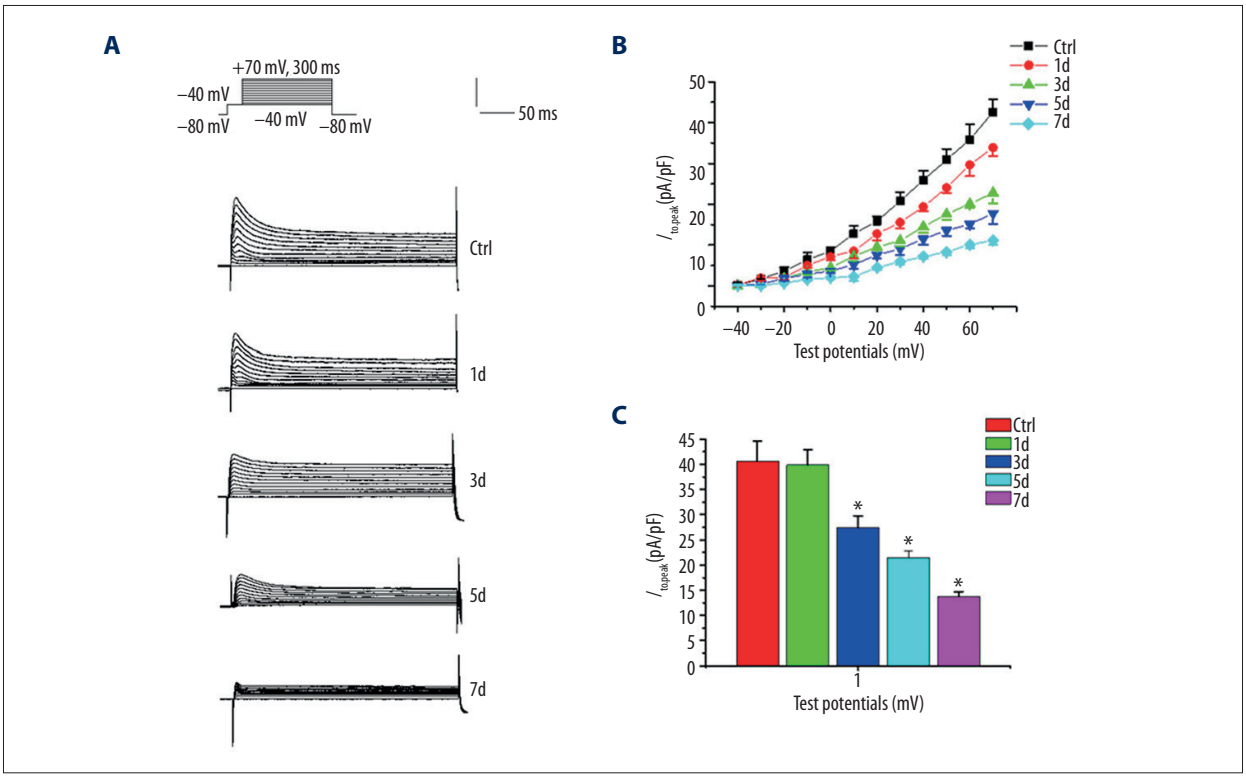

Figure 2. Comparison of the I_{to} currents in SD and control groups. (**A**): Original recording of I_{to}. The left inset shows current traces obtained by applying train pulses from –40mV to +70mV for 300 ms from holding potential of –80 mV. Current amplitudes in 3, 5, and 7 days SD groups were markedly smaller than in 1 day SD group and Ctrl group; (**B**): *I–V* relationship curves of I_{to}. $_{to}$ current were activated in the –20 mv, and shifted to depolarization. Compared with the Ctrl group, densities of I_{to} in 3, 5, and 7 days SD groups were markedly decreased; (**C**): Current-voltage relationship shows that densities of $_{to}$ increased slower at more positive membrane potentials. * P<0.01 *vs.* Ctrl group (n=18) Ctrl: control group; $I_{to,\ peak}$: the peak current of I_{to}.

and 13.24±0.56 ms), were longer than the 1 day SD group (5.77±0.20 ms) and control group (5.66±0.16 ms, P<0.01, n=18). The APD_{50} values of the 3, 5, and 7 days SD groups changed from 52.77±3.20 ms (1 day group), to 65.28±5.30 ms, 83.56±7.32 ms, and 89.24±5.56 ms. These results demonstrated that both the APD_{20} and APD_{50} were prolonged after sleep deprivation (Table 1).

Effects of sleep deprivation on I_{to} current

In Figure 2A, the left inset shows I_{to} current traces obtained by applying train pulses. Current amplitudes of 3, 5, 7, days SD groups were markedly smaller than the 1 day SD group and control group. At test potentials of +70 mV, current densities of I_{to} were 39.84±3.01 pA/pF in the 1 day group, 27.38±2.42pA/pF in the 3 days group, 21.38±1.47 pA/pF in the 5 days group, 13.74±0.98 pA/pF in the 7 days group, and 40.60±4.04 pA/pF

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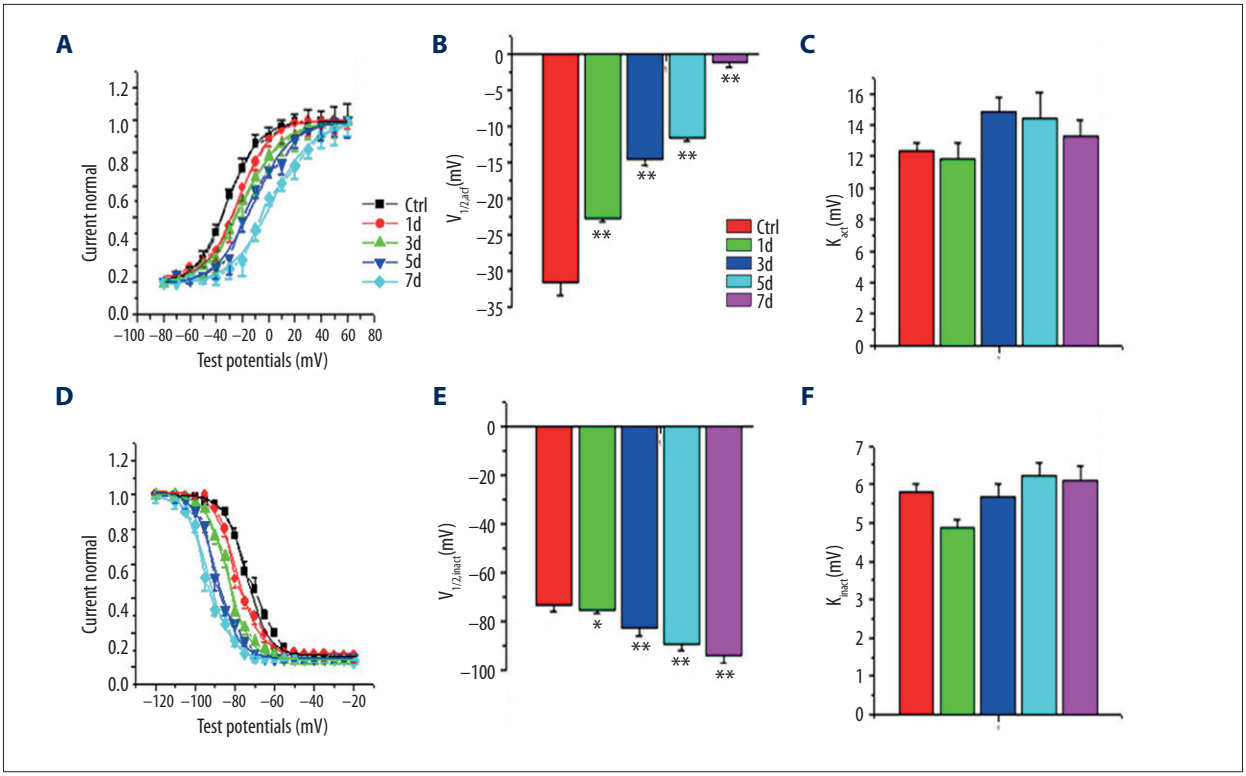

Figure 3. Voltage dependence of steady-state I_{to} activation and voltage dependence of steady-state I_{to} inactivation in the different groups. (**A**): Boltzmann equation-fitted activation curves of sleep deprivation cardiomyocytes were shifted to positive potentials; (**B**): Statistical data of $V_{1/2,act}$ were significantly changed. ** P<0.01 *vs.* Ctrl group (n=18); (**C**): The k_{act} of I_{to} activation in SD groups were not statistically changed. (**D**): The steady-state inactivated curves were shifted to depolarization; (**E**): Statistical data of $V_{1/2,inact}$ were significantly changed. * P<0.05; ** P<0.01 *vs.* Ctrl group, respectively (n=18); (F): The k_{act} of I_{to} inactivation in SD groups were not statistically changed. Ctrl: control group; $V_{1/2,inact}$: the half-inactivation potentials; k_{inact}: the slope factors of inactivation curve; $V_{1/2,act}$: the half-activation potentials; k_{act}: the slope factors of activation curve.

in the control group (P<0.01,n=18, Figure 2B). After sleep deprivation, the outwardly rectifying of I_{to} was reduced or even disappeared. In the 7 days group, the current density-voltage (I–V) curve was almost a straight line. The current-voltage relationship showed slower acceleration of densities (I_{to}) in the 3, 5, and 7 days group and a more positive membrane potential of +10 mV (Figure 2C).

Effects of sleep deprivation on steady-state activation of I_{to} currents

The changes in the I_{to} gating mechanism associated with SD have also been studied. After sleep deprivation, the steady-state activated curve was shifted to positive potentials (Figure 3A–3C). The half-activation potential ($V_{1/2,act}$) was –31.51±1.75 mV in the control group, –22.62±0.53 mV in the 1 day group, –14.47±0.86 mV in the 3 days group, –11.58±0.47 mV in the 5 days group, and –0.98±0.66mV in the 7 days group (P<0.01, n=18). The slope factors of activation curve (k_{act}) did not change significantly in any group.

Effects of sleep deprivation on steady-state inactivation of I_{to} currents

After sleep deprivation, the steady-state inactivated curve was shifted to left and the half-inactivation potentials ($V_{1/2,inact}$) of I_{to} were shifted towards depolarization. There were no changes in the slope factors of the inactivation curve (k_{inact}) (Figure 3D–3F).

Effects of sleep deprivation on the time course of recovery from inactivation of I_{to} currents

A slow recovery from inactivation of the I_{to} in sleep deprivation cardiomyocytes was obtained. Figure 4A shows that the current recovery of inactivation was slow after sleep deprivation. When recovery time was shortened to 100 ms, this phenomenon was more obvious (Figure 4B).

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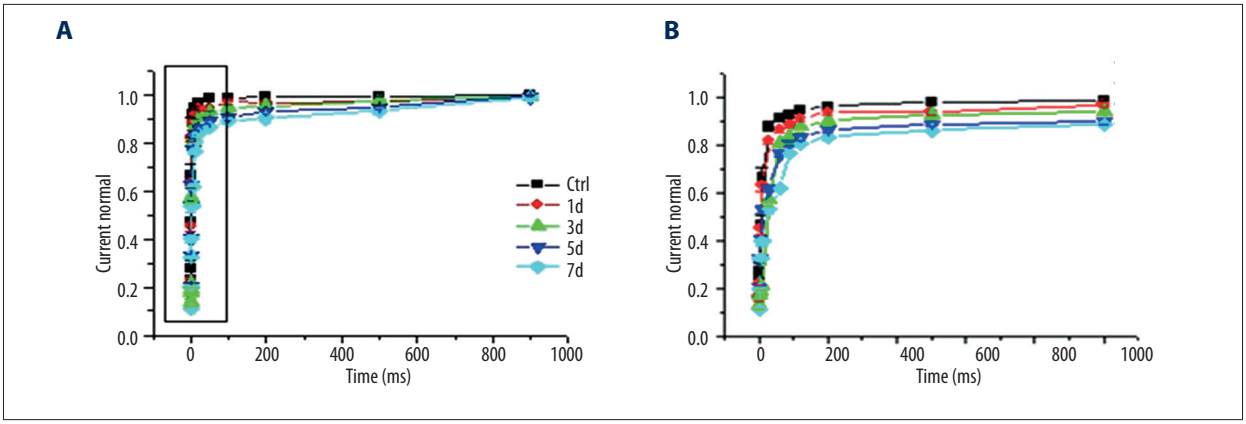

Figure 4. Effects of sleep deprivation on the time course of recovery from inactivation of I_{to} currents. (**A**): A slower recovery from inactivation of I_{to} after sleep deprivation was obtained; (**B**): the first 100 ms of recovery from inactivation of I_{to} currents (the part of the box in panel **A**). Ctrl: control group.

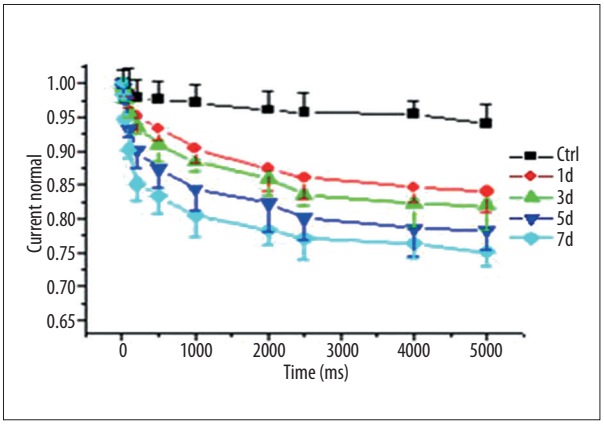

Figure 5. Comparison of closed-state inactivation of I_{to} in the different groups. Compared with Ctrl group, closed-state inactivation in sleep deprivation cardiomyocytes was accelerated. Ctrl: control group.

Effects of sleep deprivation on inactive, closed-state of I_{to} currents

The inactive, closed-state of I_{to} currents were accelerated in cardiomyocytes from sleep deprivation rats. At the 5000 ms, about 95.1% I_{to} channels were opening in cardiomyocytes of the control group, but only 80.6–84.9% of I_{to} channels were opening after sleep deprivation (Figure 5).

Discussion

To the best of our knowledge, this is the first study focused on action potential morphology changes and its possible ionic mechanism of ventricular myocyte in a rat sleep deprivation model. In this study, we first analyzed the changes of action potential traces, APD_{20} and APD_{50} of the ventricular myocytes from SD rats. This result suggested that SD significantly increased APD. Compared with the control group, the APD20 and APD50 were increased after SD. The prolongation at APD20 repolarization was more obvious than that observed at APD50. The prolongation of APD_{20} repolarization was more obvious than that of APD_{50}. The present study suggests that SD could increase APD with an obviously extended early stage of APD.

It had been widely documented that sleep deprivation (SD) leads to increased cardiovascular events, metabolic disorders, and even mortality [13–15]. Several studies of physical diseases such as chronic heart failure and obstructive sleep apnea syndrome (OSAS) have suggested a link between increased severity of sleep disturbance and risk of cardiac arrhythmias [16–18]. Investigations have indentified pathophysiological relationships between OSAS and cardiac arrhythmias, including atrial fibrillation (AF) and sudden cardiac death (SCD) [19,20]. Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by sleep fragmentation and repetitive hypoxia. The pathogenesis of cardiac arrhythmias in OSAS is believed to be multi-factorial, including hypoxia and hypercapnia, negative intrathoracic pressure, and sleep disturbance. The autonomic imbalance caused by these factors was once believed to be the final common pathway of OSA-induced cardiac arrhythmias [21–24]. Recent studies revealed that systemic inflammation, cardiac remodeling, myocardial fibrosis, and ischemia also give rise to the risk of cardiac arrhythmias in OSAS patients [25–28]. In OSAS patients, sleep deprivation is always accompanied with hypoxia and intrathoracic pressure changes. The results of OSAS studies cannot properly evaluate the independent impact of sleep deprivation on cardiac arrhythmias without interference of breathing disorders.

In addition, both human and animal studies demonstrated that paradoxical sleep loss could increase sympathetic nerve activity (SNA) and induce cardiovascular alterations, which give rise to hypertension and arrhythmia susceptibility [29–35]. Ozer

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et al. reported that young adults had significantly higher values of QTmax, QTd, and cQTd after a night of sleep debt [7]. Some research also proved prolongation of QT interval and QT interval dispersion following sleep disturbances [36,37]. A study on arrhythmia has confirmed that QT interval prolongation is associated with increased vulnerability to lethal arrhythmia such as ventricular fibrillation and sudden death[38]. Increased QTd also has been reported as a risk factor of arrhythmic events or even cardiac death [39]. The association between APD and QT interval prolongation was demonstrated by several studies under physiological and pathological conditions. Our study is the first to observe the prolongation and morphology changes of APD after sleep deprivation. Our results suggest that increased APD (especially APD_{20}) of ventricular myocytes may be a cellular mechanism of QT interval prolongation after sleep deprivation, which leads to increased risk of ventricular arrhythmia.

The I_{to} channel is a transient outward potassium current. It is a feature that is rapidly activated and inactivated in response to depolarization, which is sensitive to 4-aminopyridine [40]. I_{to} is the key outward potassium current in the early stage of action potential, and its inhibition would significantly prolong the effective refractory period (ERP) [41,42]. In the present study, we showed that SD was associated with reduction of I_{to} amplitude in cardiomyocytes, compared with the control group. The peak I_{to} current density decreased in ventricular myocytes from sleep-deprived rats, which suggests that sleep deprivation reduces I_{to} current. The current-voltage relation curve of I_{to} peak current shifted downward after sleep deprivation, which indicates that sleep deprivation decreased or even blocked the outward currents of I_{to}. The right-shifted steady-state activation curve of I_{to} after sleep deprivation suggests that SD reduced current amplitude and density by decreasing ion channel activation of I_{to}. The steady-state inactivation curves of I_{o} in ventricular myocytes from sleep-deprived rats shifted to the left, which suggests that SD might enhance the blockade of I_{to} channel and decrease the transient outward K^+ current. The retarded recovery time of inactivated I_{to} channel indicates decreased I_{to} current density, which might be related to the retarded recovery of inactivated I_{to} channel caused by SD. Facilitating the closed-state inactivation of I_{to} channel resulted in decreased I_{to} current density in ventricular myocytes from sleep-deprived rats. Taken together, the feature of I_{to} inhibition is in line with the prolongation of APD (especially APD_{20}) after SD.

Our experimental results show that I_{to} current was significantly inhibited after sleep deprivation. Some studies have confirmed that sleep deprivation can lead to cardiovascular system damage by factors such as oxidative stress, inflammation, and sympathetic nervous system activity [43–46]. Moreover, in myocardial infarction rats, I_{to} downregulation was induced by both hypoxia and the decrease of pH, and the current densities of I_{to} reduced with decreased expressions of $K_{v4.2}$ [47]. Calcineurin and NFATc3 signaling pathways contributed to the loss of heterogeneous $K_{v4.2}$ expression and reduced I_{to} density in the mouse left ventricle during chronic β adrenergic receptor agonist isoproterenol stimulation [48]. Fernández-Velasco et al. [49] found that TNF-exposure, through iNOS induction and generation of oxidant species, decreased I_{to} and prolonged action potential duration in rat ventricular myocytes. Our previous studies also have suggested that oxidative stress was associated with electric remodeling in atrial myocytes. H_2O_2 could reduce the peak current density of I_{to} and made the *I–V* curve shift downward [50]. Therefore, the results of our current experiment indicated that sleep deprivation might decrease I_{to} current by modulating autonomic nervous and hormone balances, inducing oxidative stress and the inflammatory response.

In conclusion, we suggest that inhibition of the I_{to} channel and prolongation of APD in ventricular myocytes might be important ionic and cellular mechanisms of SD-related ventricular arrhythmias.

Limitations

In the present study, we only focused on the changes of I_{to} current density and its impact on the action potential configuration after sleep deprivation. Sallé et al. suggested that the Ca^{2+} current was also involved in the lengthening of APD [51]. We plan to investigate Ca^{2+} current changes after SD in our future work. Additionally, we evaluated the electrophysiologic changes of ventricular myocytes after acute sleep deprivation in this study, but more work is needed in the field of chronic sleep deprivation.

Conclusions

Our study shows that decreased activation and accelerated inactivation of the I_{to} channel caused the reduction of I_{to} current density after sleep deprivation, which resulted in prolonged APD of ventricular myocytes.

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