

# Effect of $\text{Fe}_3\text{O}_4$ -magnetic nanoparticles on acute exercise enhanced $\text{KCNQ}_1$ expression in mouse cardiac muscle

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**Abstract:** While the potential impact of magnetic nanoparticles (MNPs) has been widely explored in almost all medical fields, including cardiology, one question remains; that is whether MNPs interfere with cardiac physiological processes such as the expression and function of ion channels, especially *in vivo*.  $\text{KCNQ}_1$  channels are richly expressed in cardiac myocytes and are critical to the repolarization of cardiac myocytes. In this study, we evaluated the effects of  $\text{Fe}_3\text{O}_4$ -magnetic nanoparticles (MNPs- $\text{Fe}_3\text{O}_4$ ) on the expression of  $\text{KCNQ}_1$  in cardiac muscle of mice at rest and at different times following a single bout of swimming (SBS). Firstly, we demonstrated that the expression levels of  $\text{KCNQ}_1$  channels are significantly up-regulated in mice following a SBS by means of reverse transcription polymerase chain reaction (RT-PCR) and western-blot. After treating mice with normal saline or pure MNPs- $\text{Fe}_3\text{O}_4$  separately, we studied the potential effect of MNPs- $\text{Fe}_3\text{O}_4$  on the expression profile of  $\text{KCNQ}_1$  in mouse cardiac muscle following a SBS. A SBS increased the transcription of  $\text{KCNQ}_1$  at 3 hours post exercise (3PE)  $164\% \pm 24\%$  and at 12 hours post exercise (12PE) by  $159\% \pm 23\%$  ( $P < 0.05$ ), and up-regulated  $\text{KCNQ}_1$  protein  $161\% \pm 27\%$  at 12PE ( $P < 0.05$ ) in saline mice. In MNPs- $\text{Fe}_3\text{O}_4$  mice,  $\text{KCNQ}_1$  mRNA increased by  $151\% \pm 14\%$  and  $147\% \pm 12\%$  at 3 and 12 PE, respectively ( $P < 0.05$ ). Meanwhile, an increase of  $152\% \pm 14\%$  in  $\text{KCNQ}_1$  protein was also detected at by 12PE. These results indicated that the administration of MNPs- $\text{Fe}_3\text{O}_4$  did not cause any apparent effects on the expression profile of  $\text{KCNQ}_1$  in rested or exercised mice cardiac muscle. Our studies suggest a novel path of  $\text{KCNQ}_1$  current adaptations in the heart during physical exercise and in addition provide some useful information for the biomedical application of MNPs which are imperative to advance nanomedicine.

**Keywords:**  $\text{KCNQ}_1$ , cardiac muscle, magnetic nanoparticles of  $\text{Fe}_3\text{O}_4$

## Introduction

Nanotechnology is at the leading edge of the rapidly developing, new therapeutic and diagnostic concepts in all areas of medicine.<sup>1</sup> Nanoscale materials are a broadly defined set of substances in which at least one critical dimension is less than 100 nanometers.<sup>2</sup> The unique ability of magnetic nanoparticles (MNPs) to be functionalized with bioactive agents and respond to a magnetic field has made them a useful tool for: magnetic resonance imaging; targeted drug and gene delivery; magnetic hyperthermia cancer therapy; tissue engineering, and cell tracking to name a few.<sup>3-5</sup> Our previous study also proposed that daunorubicin-loaded magnetic nanoparticles of  $\text{Fe}_3\text{O}_4$  (MNPs- $\text{Fe}_3\text{O}_4$ ) can overcome the multi-drug resistance of certain carcinoma cells, both *in vitro* and *in vivo*.<sup>6-8</sup> While mounting evidence suggests that MNPs have numerous advanced applications and the benefits of nanotechnology are widely publicized, *in vivo* data on

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the potential effects of pure MNPs on mammals are limited. An understanding of the interface between the MNPs and specific organs, for to their application and safety, are imperative to advance nanomedicine. Although there are several reports showing that MNPs may be accumulated in tissues when administered at clinically relevant concentrations, via relevant routes, show unremarkable histological changes in vital organs, suggesting their safety in the respective formulations to some degree.<sup>9,10</sup> However information on the physiological function of vital organs after the administration of MNPs is rarely reported.

The heart is a rhythmic electro-mechanical pump, the functioning of which depends on action potential (AP) generation and propagation, followed by relaxation and a period of refractoriness until the next impulse is generated. Cardiac repolarization is a key cellular function. Disruption of cardiac repolarization leads to potentially lethal ventricular tachyarrhythmias. Delayed rectifier  $K^+$  current ( $I_K$ ) is the major outward current involved in ventricular repolarization. Two components of  $I_K$ , the rapid voltage-gated potassium current,  $I_{Kr}$ , and slow voltage-gated potassium current,  $I_{Ks}$ , have been identified. A prolongation of APs under a variety of conditions would favor the activation of  $I_{Ks}$  so as to prevent excessive repolarization delay, causing early depolarization. The pore-forming subunit of the voltage-dependent  $K^+$  channel underlying  $I_{Ks}$  is KCNQ1.<sup>11</sup>

The KCNQ1 is a 6-transmembrane protein that can either form a functional homomeric potassium channel or coassemble with the single transmembrane domain protein encoded by the KCNE family of genes to form a heteromeric channel, the slow voltage-gated potassium channel ( $I_{Ks}$  channel).<sup>12,13</sup> Mutations in the cardiac KCNQ1 have been linked to the long QT syndrome (LQTS), which predisposes patients to arrhythmia during exercise and emotional stress, conditions that involve high levels of sympathetic nervous system activity.<sup>14,15</sup>

Stimulation of the sympathetic nervous system (SNS) in response to exercise or emotional stress results in a rapid and dramatic increase in heart rate. To ensure adequate diastolic filling time between beats, the ventricular action potential duration (APD) exhibits a concomitant shortening at the cellular level, which results in a reduction in the corresponding QT interval of the electrocardiography (ECG). The enhancement of slow voltage-gated potassium current  $I_{Ks}$  plays a major role in this process.<sup>16</sup> Although some reports show that the activity of  $I_{Ks}$  channel can be upregulated in the face of elevated SNS activity.<sup>16,17</sup> It is currently unknown whether the remodeling of  $I_{Ks}$  channel expression may be induced by the stimulation of exercise.

In this study, we investigated the expression profile of KCNQ1 in mouse cardiac muscle following a single bout of swimming (SBS). In order to assess the potential effects of pure MNPs on mammal heart, we also treated mice with normal saline or MNPs- $Fe_3O_4$  separately and then examined the effects of MNPs- $Fe_3O_4$  on the expression of KCNQ1 in exercised and non-exercised mouse heart. MNPs- $Fe_3O_4$  have not been found to downregulate the apoptosis-associated genes in certain carcinoma cells.<sup>7</sup>

## Material and methods

### Preparation of MNPs- $Fe_3O_4$

MNPs- $Fe_3O_4$  were produced by electrochemical deposition under oxidizing conditions in a 0.1 mol/L tetraheptylammonium-2-propanol solution, in which the magnetization and particle size of MNPs- $Fe_3O_4$  were found to be  $25.6 \times 10^{-3}$  emu/mg and 30 nm, respectively.<sup>18</sup> The deposited clusters were capped with tetraheptylammonium-2-propanol, which acts as a stabilizer of the colloidal nanocrystallites.<sup>19</sup> Before being applied in this experiment, the magnetized nanoparticles of  $Fe_3O_4$  were well distributed in 0.9% NaCl solution by using ultrasound treatment in order to obtain colloidal suspension of MNPs- $Fe_3O_4$ .<sup>18</sup>

### Animals

Four-week-old, male BALB/c-nu/nu mice were purchased from Beijing National Center for Laboratory Animals, the Chinese Academy of Medical Sciences prior to the beginning of our experiments. Both food and water were provided *ad libitum*.

### Exercise protocols

Forty-two mice were randomly assigned to either the non-exercised control group ( $n = 6$ ) or exercise groups ( $n = 36$ ). Thirty-six mice were placed into plastic cylinders (23 cm tall  $\times$  14 cm diameter) containing water (22–24°C) filled to a depth of 15 cm for a 30-minute swim. Non-exercised controls were kept in their home cage for the duration of the test. Mice completing the exercise were euthanized via cervical dislocation immediately or at 1, 3, 6, 12, or 24 hour after exercise. Until euthanasia, food and water were provided *ad libitum*. The ventricles were quickly dissected from each mouse, frozen in liquid nitrogen, and stored at  $-80^\circ\text{C}$  until assayed.

For the study of the MNPs- $Fe_3O_4$ , 48 mice were assigned randomly into 2 groups ( $n = 24$ ) and treated with normal saline 0.2 mL or MNPs- $Fe_3O_4$  (0.2 mL, 0.58 mg/kg) every other day for 14 day by vena caudalis injection, respectively.

**Table 1** Number of mice in each group for the study of the MNPs-Fe<sub>3</sub>O<sub>4</sub>

Groups	Treated with saline (n)	Treated with MNPs-Fe <sub>3</sub> O <sub>4</sub> (n)
Non-exercised control group	6	6
Exercise groups		
Euthanized at 3PE	6	6
Euthanized at 12PE	6	6
Euthanized at 24PE	6	6

Abbreviation: PE, post exercise.

Mice treated with normal saline or MNPs-Fe<sub>3</sub>O<sub>4</sub> were then randomly assigned to either non-exercised control group (n = 6) or the exercise groups (n = 18) respectively. Mice were exposed to a 30-minute swim 1 day after the last injection. All experiments were conducted at approximately the same time of day. After completing the exercise the mice were euthanized via cervical dislocation at 3, 12, or 24 hour after exercise (Table 1). Until euthanasia, food and water were provided *ad libitum*.

## Semiquantitative polymerase chain reaction (PCR)

The dissected left ventricles were crushed into a fine powder using a mortar and pestle. Total RNA was extracted using TRIzol® (Invitrogen, Carlsbad, CA, USA), and RNA concentrations were determined spectrophotometrically at 260 nm. RNA was treated with DNase to eliminate potential genomic DNA contamination, and reverse transcription and polymerase chain reaction (PCR) were performed with 1 µg of total RNA using ReverTraAce® a (Toyobo, Osaka, Japan). cDNAs were amplified by PCR in a Bio-Rad Mycycler thermal cycler. PCR was undertaken with triplicate samples prepared from each animal, in each group. Each reaction contained 500 ng cDNA. The PCR primers used were as: KCNQ<sub>1</sub> (525bp) forward primer, 5'-CACTTCACCGTCTT CCTCATT-3'; reverse, 5'-TCTGCGTAGC TGCCAAACT-3'; β-actin (360bp) forward primer, 5'-TTGCAGCTCCTT C GTTGCCG-3'; reverse, 5'-GCCTCGGTG AGCAGCACAGG-3'. Cycle times used for each primer pair were within the linear increase in PCR product. PCR products were separated and visualized in 1.5% agarose gels with ethidium bromide. Band intensities of KCNQ<sub>1</sub> were quantitated using ImageQuant™ software and normalized to β-actin.

## Western blot analysis

Left ventricular tissue was homogenized with 500 µL lysis buffer (100 mM/L Tris [pH 6.8], 4% sodium dodecyl

sulfate [SDS], 20% glycerol) containing the protease inhibitor phenylmethanesulfonyl fluoride 0.1 mM/L. We separated 50 µg of proteins on SDS–polyacrylamide gel electrophoresis 10%. Proteins were transferred to nitrocellulose membrane (Bio-Rad Laboratories, Hercules, CA, USA) blocked with 5% dry milk and exposed to rabbit polyclonal antibody anti-KCNQ1 (H-130: sc-20816, [Santa Cruz Biotechnology, Santa Cruz, CA USA]; dilution 1:2,000 in bovine serum albumin (BSA) 5%), rabbit polyclonal antibody anti-β-actin (ab8227, [Abcam, Cambridge, MA, USA]; dilution 1:5,000 in BSA 5%). Immunodetection was accomplished using goat anti-rabbit IgG (Sigma-Aldrich, St. Louis, MO, USA) secondary antibodies (dilution 1:4,000 in BSA 5%), and a chemiluminescence kit (Amersham Biosciences, Little Chalfont, Buckinghamshire, UK). Band intensities were analyzed by densitometry. Band intensities of KCNQ<sub>1</sub> were normalized to β-actin.

## Statistical analysis

All data are expressed as means ± SE. The effect of swimming on expression of KCNQ<sub>1</sub> was analyzed using one-way analysis of variance (ANOVA). Two-way ANOVA was used for Fe<sub>3</sub>O<sub>4</sub> administration studies.

## Results

### Acute exercise enhanced KCNQ<sub>1</sub> mRNA and protein expression in mouse cardiac muscle

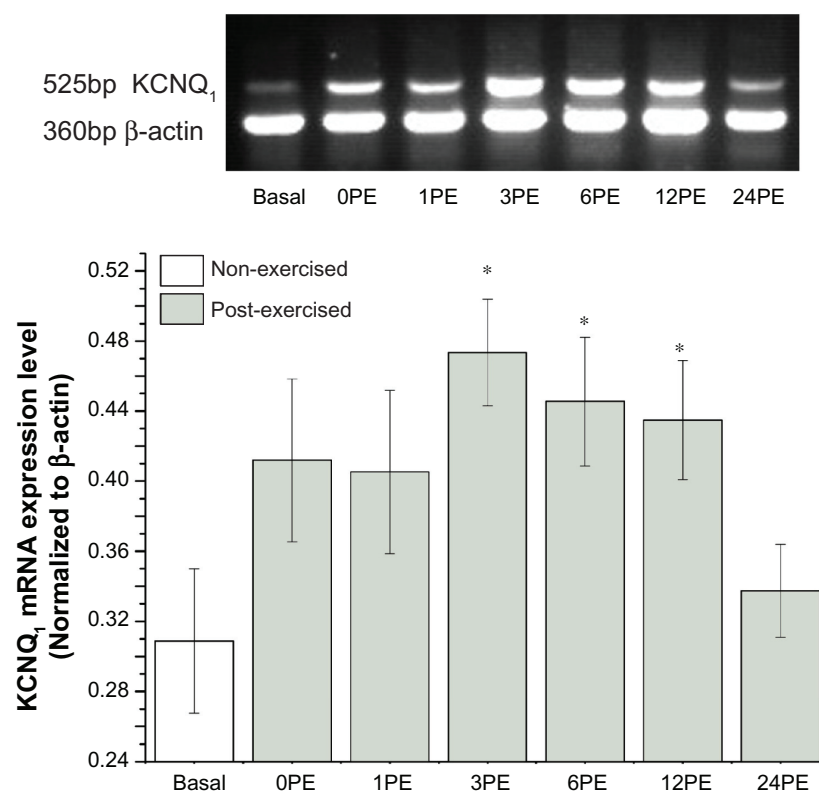
Compared to mice in the non-exercise control group (basal), a 30-minute single bout of swimming enhanced the transcription of KCNQ<sub>1</sub> mRNA in the heart at 3, 6, and 12 hour post exercise (PE) ( $P < 0.05$ , Figure 1). The expression level of KCNQ<sub>1</sub> mRNA returned to approximately control levels within 24-PE.

Expression of KCNQ<sub>1</sub> protein significantly increased with exercise in mice at 12PE compared with the non-exercised basal animals ( $P < 0.05$ , Figure 2), and the amount of KCNQ<sub>1</sub> protein decreased nearly to base level at 24PE.

### Effect of Fe<sub>3</sub>O<sub>4</sub> magnetic nanoparticles on acute exercise enhanced KCNQ<sub>1</sub> expression in mouse cardiac muscle

Over the course of the 14-day treatment with normal saline or MNPs-Fe<sub>3</sub>O<sub>4</sub>, mice showed no significant health problems. Drug administration also did not appear to affect exercise performance.

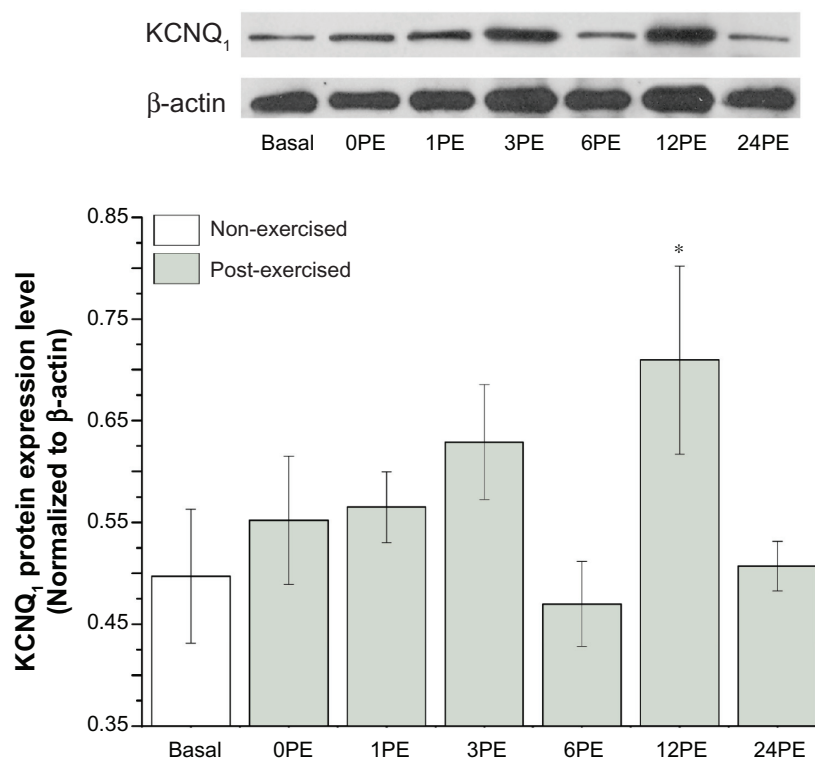
The amount of KCNQ<sub>1</sub> mRNA increased significantly at 3PE and 12PE compared to basal animals ( $P < 0.05$ ) both in



**Figure 1** Effect of a single bout of exercise on the transcription of KCNQ<sub>1</sub> mRNA.

**Notes:** All values are reported as means  $\pm$  SE (n = 6). \* $P < 0.05$ , the expression levels of KCNQ<sub>1</sub> at 3PE, 6PE and 12PE were significantly different from the basal group.

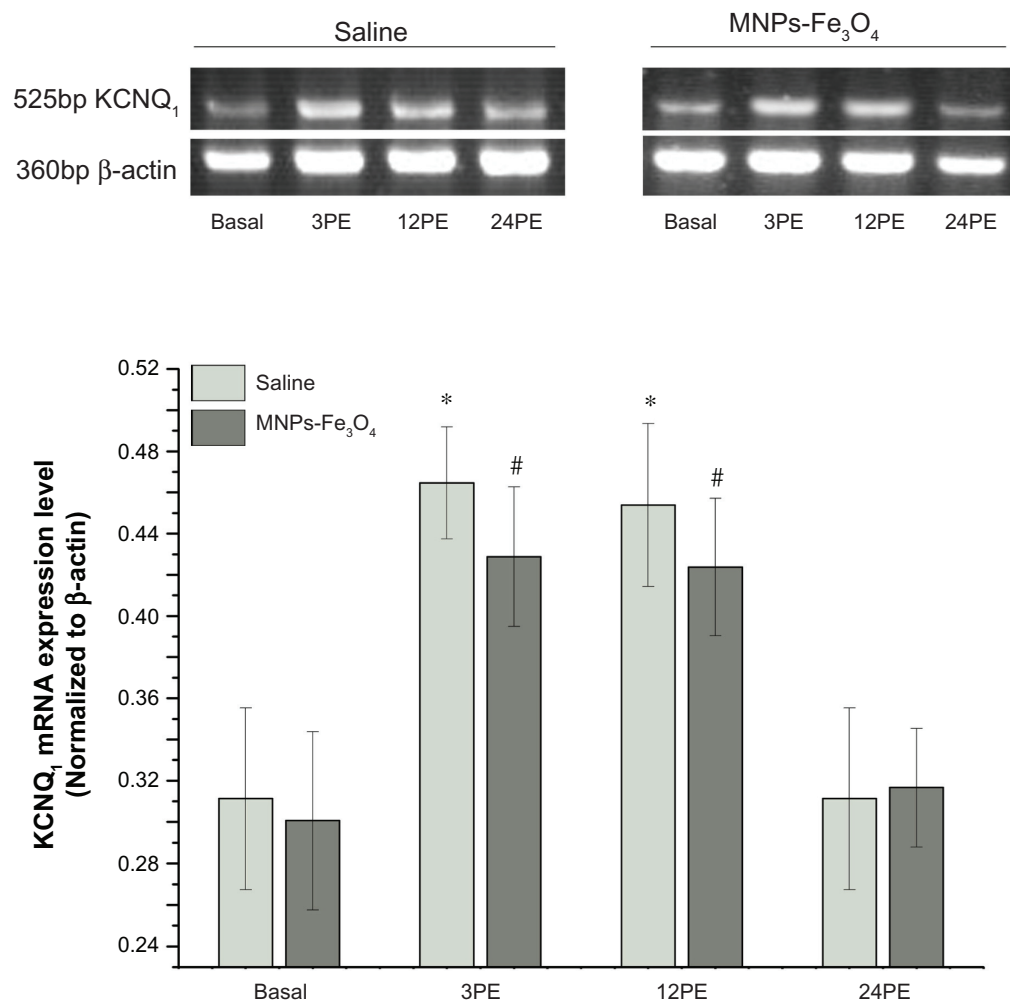
**Abbreviation:** PE, post exercise.



**Figure 2** Effect of a single bout of exercise on the expression of KCNQ<sub>1</sub> protein.

**Notes:** All values are reported as means  $\pm$  SE (n = 6). \* $P < 0.05$ , the expression level of KCNQ<sub>1</sub> at 12PE was significantly different from the basal group.

**Abbreviation:** PE, post exercise.



**Figure 3** Effect of Fe<sub>3</sub>O<sub>4</sub>-magnetic nanoparticles on the transcription of acute exercise enhanced KCNQ<sub>1</sub> mRNA in mouse cardiac muscle.

**Notes:** All values are reported as means  $\pm$  SE (n = 6). \**P* < 0.05, the transcriptions level of KCNQ<sub>1</sub> at 3PE and 12PE in saline mouse was significantly different from the basal group. #*P* < 0.05, the transcriptions level of KCNQ<sub>1</sub> at 3PE and 12PE in mouse treated with MNPs-Fe<sub>3</sub>O<sub>4</sub> were significantly different from the basal group.

**Abbreviation:** PE, post exercise.

saline and MNPs-Fe<sub>3</sub>O<sub>4</sub> group (Figure 3, Table 2). Expression of KCNQ<sub>1</sub> protein also increased significantly at 12PE when compared to basal animals (*P* < 0.05) both in saline and MNPs-Fe<sub>3</sub>O<sub>4</sub> group (Figure 4, Table 2).

No significant differences were found in KCNQ<sub>1</sub> expression profile between MNPs-Fe<sub>3</sub>O<sub>4</sub> mice and control saline mice at rest or post exercise (Figures 3 and 4, Table 2).

## Discussion

The present study examined firstly the effect of a single bout of swimming on the expression of KCNQ<sub>1</sub> in mouse cardiac muscle. Our data shows a 30-minute bout of swimming enhanced KCNQ<sub>1</sub> expression at 3PE and 12PE. Administrations of MNPs-Fe<sub>3</sub>O<sub>4</sub> had no significant influence or enhancement effect of acute exercise on KCNQ<sub>1</sub> expression in mouse cardiac muscle.

Cardiac APs are driven by ionic currents flowing through specific channels and exchangers across cardiomyocyte membranes. Voltage-gated K<sup>+</sup> currents play a major role in repolarization of APs. KCNQ<sub>1</sub> is a 6-transmembrane domain protein that can form the slow voltage-gated potassium channel (*I<sub>Ks</sub>* channel) constituting the slowly activating potassium current *I<sub>Ks</sub>*. There is a growing number of studies that suggest that the *I<sub>Ks</sub>* is important for AP repolarization and APD adaptation to changes in heart rate.<sup>16,17</sup> The importance of the KCNQ<sub>1</sub> channel at fast heart rates is especially evident from the fact that exercise or emotional stress conditions, which involve high levels of beta-adrenergic stimulation, trigger arrhythmias in more than 80% of patients with the long QT syndrome (LQTS) which arise from mutations in KCNQ<sub>1</sub>.<sup>20</sup> The activation of β-adrenergic receptors can regulate select ion channel proteins via cAMP-dependent protein kinase A (PKA) or by direct binding of cAMP to channel subunits.



**Table 2** Effect of MNPs-Fe<sub>3</sub>O<sub>4</sub> on change of KCNQ<sub>1</sub> expression in mouse cardiac muscle

Group	Change of KCNQ <sub>1</sub> mRNA (%)			Change of KCNQ <sub>1</sub> protein (%)		
	Saline	MNPs-Fe <sub>3</sub> O <sub>4</sub>	P value	Saline	MNPs-Fe <sub>3</sub> O <sub>4</sub>	P value
3PE	164 ± 24	151 ± 14	0.64	129 ± 11	136 ± 21	0.80
12PE	159 ± 23	147 ± 12	0.66	161 ± 27	152 ± 14	0.76
24PE	119 ± 17	110 ± 10	0.67	112 ± 9	116 ± 15	0.84

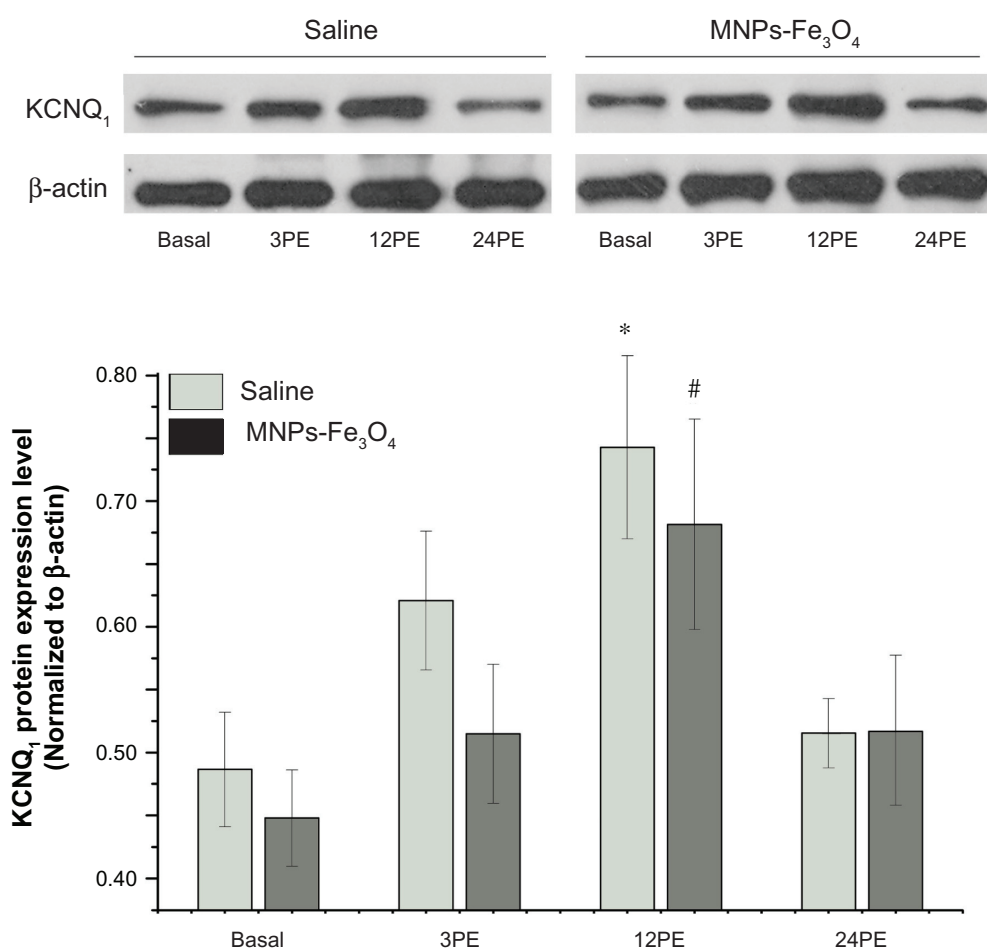
**Notes:** All values of change are compared to corresponding basal and are reported as means ± SE (n = 6). *P* > 0.05. *P* values are for comparison of MNPs-Fe<sub>3</sub>O<sub>4</sub> group with corresponding saline group.

**Abbreviations:** SE, standard error; PE, post exercise.

One key substrate for PKA-dependent phosphorylation in the regulation of the cardiac action potentials is the *I<sub>Ks</sub>* channel.<sup>21</sup> Augmentation of *I<sub>Ks</sub>* current by β-adrenergic stimulation plays an important role in mediating cardiac electrophysiological response during exercise and emotional stress.<sup>16</sup> Despite the elucidation of the macromolecular signaling complex and striking clinical data, the possibility that exercise might induce remodeling of *I<sub>Ks</sub>* channel expression has not been tested.

Our present results show that the transcription and expression of KCNQ<sub>1</sub> are increased following a 30-minute swimming. These data indicate the remodeling of KCNQ<sub>1</sub> expression that might partially compensate for the shortening of cardiac action potential duration; which results in a reduction in the corresponding QT interval of the electrocardiogram.<sup>22</sup>

The potential benefits of nanotechnology in medicine are inevitable, owing to refined, highly targeted: blood-brain

**Figure 4** Effect of Fe<sub>3</sub>O<sub>4</sub>-magnetic nanoparticles on the expression of acute exercise enhanced KCNQ<sub>1</sub> protein in mouse cardiac muscle.

**Notes:** All values are reported as means ± SE (n = 6). \**P* < 0.05, the expression level of KCNQ<sub>1</sub> at 12PE in saline mouse was significantly different from the basal group.

#*P* < 0.05, the expression level of KCNQ<sub>1</sub> protein at 12PE in mouse treated with MNPs-Fe<sub>3</sub>O<sub>4</sub> was significantly different from the basal group.

**Abbreviation:** PE, post exercise.

barrier-crossing drug delivery and imaging platforms; unique transfection; labeling and bioseparation, together with analytical and tissue engineering approaches. The versatility of MNPs is due to their capability of responding to an external magnetic field and can be functionalized with bioactive agents at the same time and/or differentially.<sup>23</sup> For successful application of MNPs, it is essential to understand the real effect of the pure MNPs on vital organs and cells.

MNP size, charge, surface chemistry and route of delivery each influence their effective time and biodistribution patterns in the body.<sup>25</sup> Large (>200 nm) particles are usually sequestered by the spleen via mechanical filtration followed by phagocytosis, whereas smaller (<10 nm) particles are rapidly removed through extravasation and renal clearance, with particles 10–100 nm believed to be optimal for intravenous administration.<sup>25</sup> In this study, pure MNPs-Fe<sub>3</sub>O<sub>4</sub> (30 nm) were used for the evaluation of their potential effect on the protein expression in the heart as well as exercise ability. The results showed that pure MNPs did not cause any apparent effects on swimming behavior nor in the KCNQ<sub>1</sub> expression profile before or after exercise.

## Conclusion

In conclusion, our results indicate a novel path of  $I_{Ks}$  current adaptations in the heart during physical exercise. Compared with mice in the non-exercise control group expression of KCNQ<sub>1</sub> in the heart were significantly increased following exercise. Therefore, not only the increased activity but also the enhanced expression of KCNQ<sub>1</sub> channel might contribute to current MNP-Fe<sub>3</sub>O<sub>4</sub> adaptations in the face of elevated sympathetic nervous system activity. Further study shows that the administration of MNPs-Fe<sub>3</sub>O<sub>4</sub> has no significant influence on the expression profile of KCNQ<sub>1</sub> in rested or in exercised mice cardiac muscle. These data might provide some useful information required to improve MNP formulations and biomedical applications which are imperative to advance nanomedicine.

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## Disclosures

The authors report no conflicts of interest relevant to this study.

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