to study on the nanoparticles aiming the inhibitory effects of HL-60/ADR cells, and the mechanism of reversing tumor MDR.

Objective Prepared “arsenic trioxide - tetrandrinebifuncnationl double combination of molecular” on targeted drug delivery system by PLGA and MPEG modified PLGA as carrier. Studied the safety evaluation of nanoparticles and the release ability of nanoparticles in vitro and the comparison of the drug release ability before and after modification. Evaluated the pharmacokinetics of the administration of rat tail vein.Investigated the effects of nanoparticles on apoptosis and cycle of acute promyelocytic leukemia (HL-60) cells in vitro.

Materials and methods Screened the effective concentration range of As2O3 and TET against tumor cells in vitro by MTT, and to determine the optimal proportion of HL-60. Prepared As2O3-TET-PLGA-NPS and As2O3-TET-MPEG-PLGA-NPS.Analysed the release profiles of As2O3-TET-PLGA-NPS or As2O3-TET-MPEG-PLGA-NPS in vitro. The fitting parameters of the non-compartmental model were obtained.The apoptosis of HL-60 cells was detected by Annexin V-FITC / PI double staining method and Hoechst 33342 staining method . The apoptosis of HL-60 cells was evaluated by MTT .The cell cycle arrest of HL-60 cells was detected by flow cytometry with PI single staining.

Results and discussion When the TET concentration is 2μg·ml-1 and As2O3 was 0.5-0.6 μg·ml-1in the concentration range,they had a synergistic effect in combination with two (Q > 1.15); when the TET concentration is 3 μg·ml-1 and As2O3 was in 0.8-1.0μg·ml-1 concentration range, they combined with a synergistic effect (Q > 1.15).As2O3-TET-PLGA-NPS lyophilization injection with an average diameter of 84.66nm, PDI was 0.132, Zeta potential was -7.5mV. As2O3-TET-MPEG-PLGA-NPS lyophilization injection with an average diameter of 66.21nm, PDI is 0.178, Zeta potential is -0.701mV. The average encapsulation efficiency was 86.18% and the drug loading was about 10.49%.According to the analysis of the experimental results of dynamic agents, we found that the release effect of As2O3-TET-MPEG-PLGA-NPS compared to As2O3-TET-PLGA-NPS had higher bioavailability, longer half-life and residence time in vivo.

Study on the anti-tumor effect of in vitro showed that As2O3-TET emulsion and As2O3-TET-MPEG-PLGA-NPS could effectively inhibit the growth of tumor cells, the apoptosis rate in a certain range of concentration and time dependence, and As2O3-TET-MPEG-PLGA-NPS group, the early apoptosis rate was significantly higher than that of As2O3-TET emulsion for injection group; The cell cycle were blocked in G2/M phase by As2O3-TET emulsion and As2O3-TET-MPEG-PLGA-NPS ,and nanoparticles group was better.

EFFICACY OF ELECTRO-ACUPUNCTURE PRETREATMENT IN REDUCING APOPTOSIS AND PROMOTING NEUROLOGICAL RECOVERY AFTER CEREBRAL ISCHEMIA-REPERFUSION INJURY IN RAT BY A MECHANISM OF SUPPRESSINGMPTP CHANNEL OPENING

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Objective:Electro-acupuncture (EA) pretreatment, that is, before cerebral ischemia to give repeated or single electro-acupuncture stimulation, can induce cerebral ischemic tolerance, reduce cerebral ischemia-reperfusion injury, the mechanism remainsto be further clarified.In this study, we will observe the effect of EA pretreatment on neurological function and apoptosis in ischemic penumbra after transient cerebral ischemia-reperfusion (CIR) injury, and to investigate whether the neuroprotective effect of EA pretreatment is related to up-regulation of mitochondrial Bcl-2/Bax ratio, inhibition of mPTPchannel opening, reduction of Cyt C release, and ultimately inhibition of apoptosis.

Methods:A rat model of CIR injury induced by 2h of right middle cerebral artery occlusion (MCAO) followed by 24h of reperfusion. 36 Male Sprague-Dawley rats were randomly divided into 3 groups: Sham, MCAO, and EA+MCAO (n=12). Animals in EA+MCAO group were treated with EA at GV20 6 days a week for 2 weeks prior to the induction of I/R. The degree of neurological deficit was evaluated by the modified neurological severity scores (mNSS),the apoptotic rate of cortical cells in peripheral cortex of cerebral infarction was measured by TUNEL staining,the opening of mPTPchannel in cerebral ischemic penumbra was detected by colorimetric method,and the expression of mitochondrial Bcl-2, Bax and cytoplasmic Cyt Cin cerebral ischemic penumbra were detected by Western blotat 24h after reperfusion, respectively.

Results:24h after reperfusion, mNSS was increased,the apoptotic rate in peripheral cortex of cerebral infarction was increased, the mPTP channel was exceptionally open,and the expression of mitochondrial Bcl-2, Bax and cytoplasmic Cyt C were both up-regulated in MCAO group than those in the Sham group, all the differences werestatistically significant(P<0.05); Compared with MACO group, the mNSS was reduced, the apoptotic rate in peripheral cortex of cerebral infarction was significantly decreased, the abnormal opening of the mPTP channel was suppressed, and the mitochondrial Bcl-2/Bax ratio was up-regulated, while the expression of cytoplasmic Cyt C was down-regulated in EA+MCAO group, all the differences were statistically significant(P<0.05).

Conclusion:Electro-acupuncture pretreatment can induce cerebral ischemic tolerance, inhibit cerebral ischemia-reperfusion injury in rats after CIR injury, improve neurological deficits.The potential mechanism of action is related to the up-regulation of mitochondrial Bcl-2/Bax ratio, inhibition abnormal openingof mPTPchannel,thereby reduction of Cyt C release.

Key words: cerebral ischemia-reperfusion injury; electro-acupuncture pretreatment; neurological function;apoptosis; mPTPchannel

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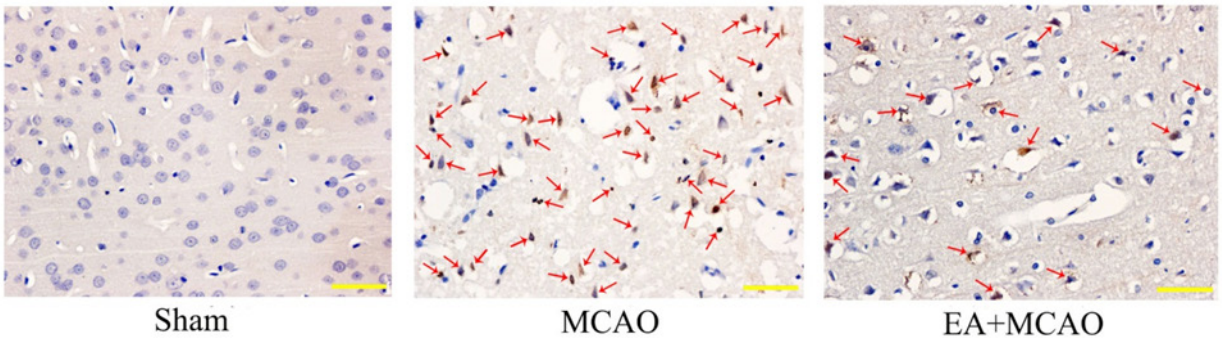

Fig.1 Expression of TUNEL positive cells in each group (10 × 40, bar scale: 50μm)

Note: The red arrows show TUNEL positive cells.

CHINMEDOMICS APPROACH TO EXPLORE THE EARLY INTERVENTION EFFECTS OF SHENG-MAI-SAN ON ALZHEIMER'S DISEASE.

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Abstract In this study, we investigated the early intervention effects of Sheng-mai-san (SMS) against d-gal combined with AlCl3 induced Alzheimer's disease (AD) in SD rats. SMS pretreatment significantly attenuated AD rats learning and memory impairment. Lipid metabolism, Carbohydrate metabolism, Vitamin metabolism and Energy metabolism were all involved in the improvement of SMS on delaying AD development. 20(R)-Ginsenoside Rh1, Schisandrin, Gominsin D, Ginsenoside Rh4, Schisandrol B, Schisantherin B, γ-Schisandrin, Schisandrin B and 6 metabolites from lignans in Schizandra Fruit may be the material base of SMS therapeutic actions. The results demonstrated that SMS exhibited significant preventive effects on AD, multi-components in SMS regulated multi-metabolic pathways may be the related mechanism.

Key words: Alzheimer's disease, Sheng-mai-san, Chinmedomics

Alzheimer's disease (AD) is a common progressive neurodegenerative disease that gradually deprives the patient of cognitive function, ability, language, visualization skills, eventually causes death1. Early intervention may be an effective means of AD prevention. Sheng-mai-san (SMS) is classic Chinese formulae composed of Ginseng (root of Panax ginseng), Ophiopogon Tuber (the enlarged part of the root of Ophiopogon japonicus) and Schizandra Fruit (the fruit of Schisandra chinensis). It has been applied for heart and blood diseases for thousand years in China and recent research showed that SMS possesses cognitive-enhancing activity2. Chinmedomics, defined as "elucidating the therapeutic and synergistic properties and metabolism of Chinese medical formulae and related metabolic pathways using modern analytical techniques" has recently demonstrated significant potential in assessing TCM3. In this study, a chinmedomics approach was applied to investigate the preventive effects and the active ingredients of SMS on AD model rats.

Objective The key metabolic pathways and the pharmacodynamic material base of SMS early intervention on AD were clarified to provide evidences for explanation of multi-components and multi-target synergistic therapeutic mechanism of SMS.

Materials and Methods Based on the d-gal combined with AlCl3 induced aging AD rats model, classic behavior test was first employed to validate the effective intervention of SMS, then Chinmedomics technology platform was introduced to reveal the active constituents in SMS and the influenced metabolic pathways.

Results and Discussion In the orientation navigation test, rats in SMS group spent less time to reach the platform on the training days compared to the model group ($p < 0.05$). SMS group reduced escape latency compared to the model group during the test ($p < 0.05$). In the spatial exploration test, rats in SMS group got higher numbers of platform crossings than in the model group ($p < 0.05$). In both of two tests, the model group and the control group were significantly different and the performance of the SMS group was more close to the control group. These results indicated that SMS treatment ameliorated cognitive deficits in AD model rats.

The metabolic profiles of plasma samples were obviously separated between SMS group and AD model group. The related metabolite biomarkers of AD disturbed by SMS interposed were including L-Lysine, Uridine, L-Leucine,