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ORIGINAL PAPER

The Neuroscience Research Institute at Peking University: A Place for the Solution of Pain and Drug Abuse

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Abstract Neuroscience research in China has undergone rapid expansion since 1980. The Neuroscience Research Institute of Peking University, one of the most active neuroscience research groups in China, was founded in 1987. Currently, the institute is overseeing four research areas, i.e., (1) pain and analgesia, (2) drug abuse and acupuncture treatment for drug addiction, (3) the mechanism of neurological degenerative disorders, and (4) the role of neuroglia in central nervous system injury. The institute is simultaneously investigating both theoretical and clinical studies. Acupuncture remains the core of research, while pain and drug abuse form the two disciplines.

Keywords Acupuncture · Pain · Drug abuse · Neuroglia

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Introduction

Neuroscience research was initiated in China in the early 1920s after the introduction of comparative anatomy of the central nervous system to China. Since then a number of Chinese neuroscientists have continued to make important contributions to this research field, such as Te-Pei Feng, Hsiang-Tung Chang, Jin-Xi Wang, Zhu Ou-Yang, etc. Neuroscience underwent a period of rapid expansion in China after 1980. There are many research groups established all over the country, but neuroscience research is grouped mainly in four cities—Beijing, Shanghai, Xi'an, and Hong Kong. Also, more and more Chinese neuroscientists have published in some important international neuroscience journals.

The Neuroscience Research Institute of Peking University is one of the most active neuroscience research groups in China. This institute stemmed from the research group on the study of the mechanisms of acupuncture analgesia, founded in 1965 in Beijing Medical College. The research group has since been developed into the Neuroscience Research Center of Beijing Medical University in 1987, the Key Laboratory for Neuroscience under the auspices of the Ministry of Public Health in 1993, the Neuroscience Research Institute in 1997, the Key Laboratory under the auspice of Ministry of Education in 2001, and Department of Neurobiology in 2001. This year denotes its 20th anniversary.

The institute was founded and has been headed by Professor Ji-Sheng Han, a member of the Chinese Academy of Sciences, the President of the Chinese Association for the Study of Pain (CASP), and the founder of the Beijing Society for Neuroscience. He has been devoted to the study of the neurochemical basis of acupuncture analgesia for more than 40 years. Aside from numerous funding from China, Professor Han has been funded by the National Institute of Drug Abuse (NIDA), USA, for research on "neurobiology of acupuncture analgesia" for 12 consecutive years, and currently by the National Center for Complementary and Alternative Medicine (NCCAM), USA for research on drug addiction. As a grantee of the National Institute of Health (NIH), USA, he was invited to lecture on the Consensus Conference on Acupuncture, sponsored by the NIH in 1997.

Currently, the institute is overseeing four research areas, i.e., pain and analgesia especially acupuncture analgesia (AA), drug abuse and acupuncture treatment for drug addiction, the mechanism of neurological degenerative disorders and the role of neuroglia in central nervous system (CNS) injury.

Pain, Analgesia, and Acupuncture Analgesia

Our main research on pain and acupuncture analgesia has received international recognition. The research extends from the macroscopical level (brain cortex and nuclei) to the microscopic and even atomic level, with crystal structure of the ion channel.

In a recent study of the neurochemical mechanisms of acupuncture analgesia, we found that: (1) while opioid systems (Han 2003, 2004) play a major role in mediating acupuncture analgesia, excitatory amino acids are also heavily involved (Choi et al. 2005; Huang et al. 2005); (2) the effect of acupuncture analgesia was observed not only in normal rats, but also in rat models of chronic pain, including neuropathic pain (Sun et al. 2004; Huang et al. 2004a) and of inflammatory pain (Huang et al. 2004b; Liu HX et al. 2007; Liu FY et al. 2007); (3) in order to analyze the genetic background of AA, we started to use mice instead of rats. The neurochemical mechanisms underlying AA in rats were also found in mice, including opioids and nocistatin (Huang et al. 2003), cholecystokinin B (CCK_B) receptor system (Huang et al.

2007), etc. In addition, we found that the efficacy of AA varies greatly in different strains of mice (Wan et al. 2001; Huang et al. 2002); (4) long-term synaptic plasticity (e.g., LTP/LTD) in the spinal dorsal horn plays a key role in the generation of neuropathic pain, and contributes to the frequency-dependent electroacupuncture (EA) analgesia (Xing et al. 2007).

At the higher level of CNS, functional magnetic resonance imaging (fMRI) technique was used to characterize the brain areas involved in mediating EA-induced analgesia in a frequency-dependent manner (Zhang et al. 2003). Deep brain multi-channel recording (Wang Y et al. 2004; Wang JY et al. 2004) was used to show the flow of pain-related information and its modulation by EA stimulation. Using this technique, we are examining the response of the CNS to acupuncture stimulation of different frequencies in an attempt to elucidate the coding of biological information from periphery to the CNS.

In the studies of the mechanism for acute and chronic pain at receptor and ion channel level, we have found that: (1) The transient receptor potential V1 (TRPV1) plays important roles in both acute pain and chronic inflammatory pain (Luo et al. 2004); (2) Hyperpolarization-activated, cyclic nucleotide-gated cation channel (HCN) plays a role in the process of central and peripheral sensitization in neuropathic pain (Tu et al. 2004; Sun et al. 2005b); (3) Ectopic discharges from the injured DRG are triggers, but do not play important roles in the maintenance of neuropathic pain (Sun et al. 2005a); (4) Protein kinase D1 and Cdk5 in primary sensory neurons and dorsal horn neurons are involved in thermal hyperalgesia in rats with inflammatory pain (Wang Y et al. 2004; Wang JY et al. 2004; Yang et al. 2007; He et al. 2007). CDK5 is also involved in the μ-opioid receptor-mediated neuroprotection from damage induced by serum deprivation (Wang et al. 2006); (5) Different subtypes of 5-HT receptors in the spinal dorsal horn play different roles in the descending control of pain (Liu HX et al. 2007; Liu FY et al. 2007); (6) In the structural insights into molecular modulation of K_v4 channels by accessory subunit KchIPs, the solved co-crystal structure revealed a unique clamping mode of the complex in which a single KChIP1 molecule as a monomer laterally clamps two neighboring $K_v4.3$ N-termini in a 4:4 manner (Wang et al. 2007).

Moreover, we are investigating the possible roles of signal transduction pathway in pain and pain modulation. We are looking into the roles of some key molecules in primary sensory neurons and astrocytes, spinal dorsal horn and the brain, which might play an important part in three different types of chronic pain (inflammatory pain, neuropathic pain, and cancer pain).

Drug Abuse and Acupuncture Treatment for Drug Addiction

Drug addiction has become a major social problem in China in the recent two decades. By applying the results obtained in pain research, we have used EA and transcutaneous acupoint stimulation (e.g., Han's acupoint nerve stimulator, HANS) device for the treatment of opiate addiction. HANS was first used for the treatment of withdrawal syndrome (physical dependence) in heroin addicts (Han et al. 1994; Wu et al. 2001; Han 2005) and the clinical data showed that HANS reduced more than 90% of the amount of buprenorphine needed by the drug addicts to complete the detoxification procedure. HANS can also effectively reduce opiate craving (psychic dependence), hence reducing the chance of relapse after detoxification (Wu et al. 1999; Han et al. 2005; Zhong et al. 2006). The success rate of keeping the former heroin addicts drug free for 1 year has been increased from less than 5% to more than 20% (Han et al. 2005).

In elucidating the mechanism of EA treatment of drug addiction, we found that: (1) 2 Hz EA could effectively suppress the expression of morphine-induced conditioned place preference (CPP) and blocked the reinstatement of extinguished CPP in the rat (Shi et al. 2003; Chen et al. 2005d); (2) EA could increase the CNS level of preproenkephlin (PPE) and

preprodynorphin (PPD) mRNA and block the dopaminergic response to both environmental cues and drug priming (Shi et al. 2004). These findings confirmed the clinical observation that EA/HANS may serve as a potential therapy in decreasing drug craving and drug relapse.

In order to explore the molecular mechanisms underlying the relapse of opiate use, we studied the possible involvement of NMDA receptor, especially the NR2B-containing NMDA receptor in the rat model of CPP. Our data indicated that the NR2B-containing NMDARs in the nucleus accumbens and the hippocampus play a significant role in mediating the reinstatement of rewarding responses to morphine exposure. Ifenprodil, an antagonist of NMDARs and highly selective to the NR2B subunit, is expected to be a prototype drug to be used for prevention of drug relapse (Ma et al. 2006, 2007). Some of the findings have been included in a chapter of the Comprehensive Textbook of *Substance Abuse* (Han et al. 2005).

Mechanisms of Neurological Degenerative Disorders—Parkinson's Disease (PD) and Alzheimer's Disease (AD)

Our studies on PD therapy using stem cells, transgenic manipulation as well as EA and Chinese herbal medicine have earned a Chinese patent (patent number ZL00107779.1). We demonstrated that: (1) EA protected dopaminergic neuron from inflammation-mediated damage in medial forebrain bundle-transected rats (Liu et al. 2004); (2) The Chinese herb Triptolide protected dopaminergic neurons from inflammation-mediated damage induced by intranigral injection of lipopolysaccharide (Zhou et al. 2005); (3) Triptolide inhibited TNF-α, IL-1β and nitric oxide production in primary microglial cultures (Zhou et al. 2003); and (4) Triptolide up-regulated NGF synthesis in rat astrocyte cultures (Xue et al. 2007).

Studies on the mechanisms of AD have revealed that: (1) Mutations in the presenilin 1 (PS1) gene are responsible for the early onset of familial Alzheimer's disease (FAD); (2) FAD-associated mutations of PS1 accelerated the production of Aβ and accumulation of Aβ42 in neurons, which caused neurodegeneration (Chui et al. 1999, 2001); (3) PS1 interacted with neurofibrillary tangles and deposited in dystrophic neurites in AD brain (Chui et al. 1998); (4) PS1 mutations contribute to the onset of AD not only by enhancing Aβ production but also by accelerating the formation and accumulation of filamentous tau (Tanemura et al. 2006); (5) The lipoprotein lipase in hippocampus may be associated with pre-synaptic vesicles and involved in the learning and memory process (Chui et al. 2007).

Role of Neuroglia in CNS Injury

Glia cells are estimated to be 10-fold as many as neurons in the brain. In order to extend our study at the NRI from a neuronal to a more neuronal-astrocytic focus, we began to work with astrocytes in both in vivo and in vitro studies. We are focusing on the role of astrocytes in brain injury and pain (Chen et al. 2003, 2005a, b, c; Yu et al. 2004). These related researches will complement the three studies with astrocytic roles in pain, drug addiction, and neurodegeneration. Recently, we found that Cdk5, a crucial protein kinase in the nervous system, plays a key role in the activation of astrocytes after mechanical injury (He et al. 2007).

Concluding Remarks

The Neuroscience Research Institute at Peking University has been evolving from a research group for the study of acupuncture analgesia in 1965 to an institute with eight principal

investigators working coherently and independently in four directions in 2005. Our institute is characterized by its translational research. Acupuncture remains the core of research, whilst pain and drug abuse form the two main sub-disciplines.

In terms of pain research, we are asking two basic questions: (1) Why acupuncture works for most, but not all subjects? (2) Why stimulation of different frequencies can trigger the production and release of different neurochemical substrates in the CNS? In terms of drug abuse research, we are also asking two questions: (1) Why psychic dependence, once formed, can remain life long? (2) How can the long term plastic changes in the reward system be normalized and brought back to normal functions?

Theoretical and clinical studies are proceeding side-by-side in our institute. While we are using various means including genetic approaches and fMRI scans to elucidate the basic pain mechanisms, we are also using the HANS device for clinical treatment of pain. Furthermore, Professor Han, the director of our institute has successfully lobbied with the Ministry of Health in setting up a separate department for Pain at major hospitals in China. In drug relapse prevention, while we are studying the details of brain reward pathways, we are also using our portable device to rehabilitate more than 20% of heroin addicts back to a drug free status for as long as 1 year. The glia cell research is gradually moving from in vitro to in vivo studies and the PD and AD research are moving from laboratory to clinical studies.

Neuroscience by its terminology ranges from neuron to behavior, from single molecule to human cognition. We fully understand that it is by no means an easy task to keep at the frontiers at both theoretical and practical facet, but we are doing our best to fill in the gap as much as we can.

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