104-11-6

Modulation Effects of Acupuncture on the Nervous System

陳易宏 教授

Abstract

Acupuncture is the stimulation of acupoints involving penetration with thin mental needles and their subsequent manipulation. Acupoints are found at specific locations of the body and most are distributed in 12 bilateral meridians and two midline channels, i.e. Du and Ren Meridians. Besides manual acupuncture (MA), electroacupuncture (EA) is a modified form of acupuncture that utilizes electrical stimulation. From the neurophysiologic point of view, acupuncture may trigger local receptors of the accupouints to send neural impulses to the spinal cord and then to the brain, to modulate the release of neurotransmitters that subsequently act on the CNS or the peripheral nerves. The transmission pathway is similar, but different to those of pain and itch. During the past decades, investigations of the mechanisms of EA analgesia have focused on the involvement of endogenous opioids in acupuncture analgesia, also called the endorphins theory. This is based on the observation that naloxone, an antagonist of the μ opioid receptor, attenuates the analgesic action of acupuncture in healthy subjects and mice. Here, we revealed a novel non-opioid mechanism of electroacupuncture -induced analgesia.

104-11-13

Translational Potential of Mood Stabilizers for Brain Disorders: What Have We Learned?

莊德茂 教授

Abstract

Most of the brain diseases still lack efficient treatments and, unfortunately, numerous obstacles exist in the development of new drugs for hard-to treat CNS disorders. Growing evidence supports the notion that expanding or repurposing the use of existing clinical drugs for brain disorders is a rational and realistic approach. In this presentation the state-of-the-art of neurobiology of the mood stabilizers lithium and valproic acid (VPA) will be reviewed. Evidence will be presented that lithium and VPA, via inhibiting glycogen synthase kinase-3 (GSK3) and histone deacetylases (HDACs) respectively, elicit a spectrum of neurophysiological events in preclinical studies. These include neuroprotective and neuroptrophic effects, anti-depressant and anti-anxiety efficacy, anti-inflammation and BBB preservation, as well as neurogenesis and angiogenesis. Specific examples to be presented are lithium-induced potentiation of ketamine's rapid antidepressant effects in a mouse model of depression, and the beneficial effects of lithium and VPA in animal models of stroke, traumatic brain injury and Huntington's disease. The role of a newly identified target of mood stabilizers, FGF-21, in treating CNS disorders will also be discussed.

104-11-27

Noise Exposure: a Risk Factor of Hypertension

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Abstract

Noise pollution is an emerging issue in public health. Many epidemiological studies have been reported the association between traffic noise exposure and cardiovascular diseases. The possible biological mechanism is that noise exposure, a psychosocial stressor, may active the sympathetic and endocrine systems to affect the humoral and metabolic states in the human body, producing the increase in blood pressure and the changes in other risk factors (such as blood lipids and glucose levels) that promote the development of hypertension and cardiovascular diseases. However, the relationship between occupational noise exposure and hypertension is inconsistent. Some studies found the positive and significant association between exposure to occupational noise and hypertension, but some did not show the significant results. Two possible reasons for this inconsistence may be the use of hearing protective devices (HPDs, such as earmuff or earplug) to cause an exposure bias and some important risk factors of hypertension (i.e., body mass index, cigarette smoking, alcohol drinking, regular exercise, salt intake and a family history of hypertension) without adjustment. In this presentation, the first study with a cross-sectional design will use the high-frequency hearing loss as a biomarker of occupational noise exposure to investigate the association between hypertension among aircraft-manufacturing workers. The second study based on a prospective cohort will apply the HPD-adjusted noise levels (i.e., inner-ear exposure) and control for some important confounders of hypertension to elucidate the casual relationship. The third study with a repeated-measurement design will measure personal noise exposure and ambulatory blood pressure simultaneously during the working and non-working days to investigate the acute effects of noise exposure on systolic blood pressure(SBP) and diastolic blood pressure(DBP) among normotensive, pre-hypertensive and hypertensive workers. These studies contribute to the conclusion that exposure to occupational noise levels is associated with the development of hypertension.

Keywords: Blood pressure, epidemiological study, hypertension, noise exposure.

104-12-11

Integration of Epidemiology and Outcome Research for Health Policy Decision

王榮德 講座教授

Abstract

There are two basic components for a decision tree: After a period of time, how much the likelihood or probability of an event of interest would be and what the consequence of the event could be. To express it in epidemiologic terms, the first component is incidence rate of how many incidences of disease of interest develop from a follow-up population time at risk, while the second component is the expected outcome of the event, or, the pay-off after the event occurs. In order to evaluate the health policy, one usually must wait for a long period of time to collect the data of long term outcome, which is quite different from other business transactions. In fact, we must generally wait for a long period of time to determine whether the person with the illness of interest would survive and whether his/her quality of life would improve. Thus, simply relying on regular survey of customer's satisfaction is insufficient to decide if a healthcare service delivered by one provider is better than the other.

To assess the long term effect or outcome of a health policy, one generally considers both the lifetime functions of survival and quality of life (QOL) along the course. Namely, one must estimate QALE (quality-adjusted life expectancy) with QALY (quality-adjusted life year) as an outcome indicator for comparison of outcomes for different illnesses or health related events. We have developed a method to combine both survival and QOL functions to estimate QALE. The lifetime survival function can be multiplied with the average cost at time t and summed up throughout life to estimate the lifetime costs for illness of interest. It can also be multiplied with the proportion of functional disability at time t and summed up lifelong to estimate the needs for long term care for a specific illness. When we subtract the QALE from age- and sex-matched referents simulated from our national life tables, we can estimate the loss-of-QALE, which is the benefit of prevention of a specific illness. All of the above quantities can be linked with incidence rate resulted from epidemiologic studies for making health policy of health promotion and prevention. In brief, methods have been developed to estimate lifetime survival functions for different illnesses. Then, one may sum up throughout life after multiplying survival function with a second function, say, QOL, cost, or proportion of disability to obtain estimates of QALE, loss-of-QALE, lifetime cost, and long-term care need for the illness of interest.

104-12-18

Discovery and Development of Natural Insulin Mimetics for Diabetes

項千芸 教授

Abstract

Diabetes mellitus is a serious chronic metabolic disorder that has a significant impact on the world health. Insulin receptor (IR) signaling transduction pathway is the principle mediator of glucose homeostasis. Although there are several drugs currently available for diabetes, insulin is still the only medicine for the treatment of type 1 diabetes and the only medicine that targets to IR. In our previous study, we have identified novel natural insulin mimetics (NIMs) from gourds, including bitter melon and trichosanthes. The amino acid sequences of NIM are totally different from those of insulin; however, NIM is able to interact with IR and bind to sites different from the insulin-binding sites on IR. After binding to IR, NIM activates IR-downstream signaling transduction pathways, stimulates the translocation of glucose transporter-4 to cell membrane, and increases the uptake of glucose in cells. Oral administration of NIM stimulates the clearance of glucose in normal and diabetic mice in a dose-dependent manner. In addition, long-term administration of NIM decreases the levels of glycated hemoglobin A1c in diabetic mice. In conclusion, the new peptide drug for diabetes which fulfills the criteria of Investigational New Drug is the goal we will achieve in the future.

104-12-25

Oxidative Stress Response in the Metabolic Reprogramming of Human Cells with Mitochondrial Dysfunction - Implication in the Pathophysiology of Mitochondrial Diseases

魏耀揮 校長

Abstract

Human cells with mitochondrial dysfunction associated with disease or aging tend to switch ATP production from aerobic metabolism to glycolysis. In the past two decades, we demonstrated that pathogenic mitochondrial DNA (mtDNA) mutations not only impair oxidative phosphorylation but also cause overproduction of reactive oxygen species (ROS). We found that sub-lethal concentrations of ROS can down-regulate mitochondrial respiration and upregulate glycolysis and the antioxidant defense system through activation of AMPK-mediated signaling pathways in human skin fibroblasts. Oxidative stress-elicited phosphorylation of AMPK, a key energy sensor, can increase the glycolytic flux and intracellular levels of NADPH and glutathione. This scenario has been also observed in primary cultures of skin fibroblasts harboring pathogenic mtDNA mutations such as A8344G transition, which is commonly found in patients with MERRF syndrome. Recently, we demonstrated that mild oxidative stress can induce acetylation of certain subunits of the respiratory enzyme complexes and down-regulate bioenergetic function of mitochondria. We found that the expression levels of Sirt3 and Sirt5 were altered in human skin fibroblasts exposed to hydrogen peroxide and in cybrids harboring pathogenic mtDNA mutations. By using immunoprecipitation and Western blotting with antibodies specific to acetyl lysine, we showed that oxidative stress could modulate the bioenergetic function of mitochondria through acylation of proteins involved in oxidative metabolism of the human cells under oxidative stress. We suggest that excess production of ROS and its subsequent activation of oxidative stress response to switch energy metabolism from respiration to glycolysis play an important role in the adaptation and survival of tissue cells in patients with mitochondrial diseases. The cultured cells harboring specific mtDNA mutations can be used for screening of natural products and compounds that may be used for development of drugs to treat human diseases associated with mitochondrial dysfunction.

Understanding DNA demethylation and reprogramming by somatic cell nuclear transfer

張 毅 講座教授

Abstract

DNA methylation is one of the best characterized epigenetic modifications. While the enzymes that methylate DNA are well-known, how DNA methylation is removed was not known till recently. In the first part of the seminar, I will summarize our efforts in the past several years in dissecting the mechanism of active DNA demethylation. I will then focus on the role of Tet/Tdg-mediated DNA demethylation in embryonic stem cells, preimplantation embryos, and primordial germ cell reprogramming.

In the second part of my seminar, I will talk about our recent efforts in identifying and overcoming an epigenetic barrier of reprogramming by somatic cell nuclear transfer (SCNT). We show that the H3K9me3 deposited by Suv39h enzymes in somatic cells prevents zygotic genome activation thus impedes development of SCNT embryos. We show that this epigenetic barrier can be overcome by injection of an mRNA encoding an H3K9me3 demethylase leading to improved developmental potential of SCNT embryos. We also show that this reprogramming barrier is conserved in human SCNT reprogramming, and that we can improve human SCNT embryo development as well as patient-specific NT-ESC derivation through injection of an mRNA encoding an H3K9me3 demethylase. This work has important implication in regenerative medicine.

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