KONFERANSLAR / CONFERENCES

Repair of CNS Injuries by Olfactory Ensheathing Cells

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ABSTRACT

The failure of severed axons to regenerate in the central nervous system disrupts connections between brain areas and cuts off the flow of information between them. This leads to severe disability which is chronic and incurable. Our concept of repair is to re-build a bridge to enable the sprouts formed by the severed nerve fibres to regrow to their original destinations and restore lost functions. We call this the pathway hypothesis. Following the discovery of the unique ability of olfactory nerve fibres to grow in adult life, electron microscopy has revealed a unique type of cell-the olfactory ensheathing cell (OEC) which provides the pathway for these fibres (Raisman, 1985). The concept behind our repair strategy is to transplant OECs from the olfactory system, where they provide a pathway for nerve fibres to grow, into an area of damage in the spinal cord where damaged nerve fibres do not grow.

Our first experimental demonstration of the reparative properties of transplanted OECs was in a unilateral lesion of the rat corticospinal tract (CST). This leads to a loss of directed reaching function by the forepaw of the operated side. Function is restored consistently by injection of OECs into the lesion, where they form a continuous bridge over which the CST fibres regenerate, become myelinated by peripheral type myelin produced by the OECs and re-enter the spinal cord to arborise caudally in the medial grey (Keyvan-Fouladi et al, 2003; Li et al, 1998).

The number of cells we can obtain from the olfactory system is limited, and we do not yet have sufficient to bridge the extensive area of damage encountered clinically in human spinal cord injury. We therefore chose to model a situation where a small number of cells, strategically placed, could be tested. This situation is brachial plexus avulsion. In clinical practice this is commonly the result of a road traffic injury in which the nerves to the arm are pulled out of the spinal cord. The affected arm is totally disabled.

To develop a rat model we demonstrated that unilateral section of all four DRs from the 6^{th} cervical to the first thoracic segments (C6 to T1) causes total loss of input from the arm measured electrophysiologically and failure of the denervated forepaw to grasp bars during a climbing test using an endogenous matrix which allows a limited amount of cells to be placed accurately and retained in sufficient numbers to bridge the lesion, we showed that transplanted OECs bridged the lesions, provided a

pathway for regenerating DR fibres to re-enter the dorsal horn and ascend in the dorsal columns, restored electrophysiological transmission into the dorsal columns and postsynaptic responses in the dorsal column nuclei and restored forepaw grasping (Ibrahim et al, 2009).

Since we could achieve structural and functional repair of two specific spinal cord and spinal root injuries in adult rats, we believe this means they can be repaired in man. The ability to restore hand function in a disabled patient would be a major factor in improving the quality of life. Learning how to obtain reparative cells from human tissue will open the way to repair not only of spinal cord and spinal root injuries, but beyond that to strokes involving fibre pathways in the brain, and damage to cranial nerves.

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From T_H1 to T_H22: Is There a Cytokine That, Really' Matters in Neuroinflammation?

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ABSTRACT

One would think that having an animal model for multiple sclerosis (MS), the therapeutic interventions in rodents should be easily translatable into human disease. In stroke, where the modeling in animals is relatively simple and straight forward, translation attempts failed miserably. Is the animal model to blame? Not at all! After systematic analysis of potential shortcomings in the preclinical data the culprit was identified as "the positive-publication bias". This means that failures and negative data are hardly publishable even though their value is at least as high as the exciting positive data found in high-impact factor journals. I will discuss, using the recent attention to "T_H17 cells" in the context of EAE, how fashion and claims can spiral out of control and mislead the design of therapeutic interventions profoundly. Specifically, during autoimmune neuro-inflammation, helper T (T_H) cells initiate tissue damage and neurological impairment. While the role of polarized T_H1 and T_H17 cells as initiators of the disease remains a subject of some debate, none of their signature cytokines is essential for the development of experimental autoimmune encephalomyelitis (the animal model of MS). The conflicting data in regards to the EAE susceptibility of mice lacking transcriptions factors such as RORγt, cytokine receptors, such as the IL-23R and cytokines such as IL-12, IFNγ and IL-27 could be resolved by the discovery that not IL-17, but another cytokine, unifies all the discrepancies and explains the role of these enigmatic "T_H17 cells" in autoimmunity and brain inflammation. I will propose such a cytokine and data solidifying the claim that there is indeed at least one non-redundant T cell-derived factor required for the development of neuroinflammation.

Reflections on a Life in Science

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ABSTRACT

During my time as a medical student I was persuaded to spend three years doing a PhD on the connections of the rat hippocampus. At that time connections were traced by making lesions. It was also a time when electron microscopy was becoming applicable to the nervous system. Prompted by discussion of my findings with my supervisor in 1965, I came to the conclusion that new synapses were forming in the adult brain. I introduced the word plasticity to describe the phenomenon. It took over ten years of struggle in the wilderness before this heretical idea became accepted.

I have spent a lifetime trying to see whether this property of nervous tissue could lead to a method for repairing injuries which are currently irreparable. They are still irreparable but it is a joy to have worked on something that could benefit people, and to have been able to shed some light on what others will in future achieve.

My work on plasticity has led to the use of olfactory ensheathing cells, and -in the last few years- to a new heresy: the pathway hypothesis. It is comforting that, even so many years later, I can put forward an idea as heretical now as plasticity was then. Science depends on hypotheses. But the accepted hypothesis is the tombstone of endeavour, the enemy of progress.

Plasticity overthrew the idea that the nervous system is anatomically fixed. Its opposite is now becoming a future topic-how is the nervous system stable. Perhaps one day it will be found that plasticity and stability are two sides of the same mechanism.

Plasticity has passed into the common vocabulary of neuroscience and neurology. But plasticity is still a young idea. It is an idea with a future. It is a property only dimly glimpsed, little understood. Beyond laboratory science and medicine, it has wider implications for the understanding of ourselves and the potential of our species.

My talk does not celebrate any achievements of mine. I was simply in the right place, at the right time, and with the right supervisor. My purpose here is to encourage those to whom the future belongs, who will see clearer than we do, and understand what is to us a mystery. To the one who is content to make a simple observation, made with clear eyes and contemplated with an honest mind, Nature waits willingly to reveal her beauties.

Genomic and Genetic Approaches to Mammalian Brain Development

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ABSTRACT

The mammalian cerebral cortex derives from progenitors present in the ventricular and subventricular zones of the embryonic dorsal telencephalon. To identifying genetic networks involved in corticogenesis we performed data mining in the www.genepaint.org gene expression database for transcripts that are restricted to cortical progenitor cells. > 1000 genes were regionally expressed in the developing neocortex and encompass a wide range of biochemical functions including transcription and cell cycle control. Cell cycle regulators expressed in proliferating neuronal progenitors include Chaf1b, Xpo1, Prim1, E2f2, Rad54, Mcm2, Mcm7, E2f2, Pbk, Kif4, Prc1, timeless and Esco2.

Esco2, an evolutionary conserved acetyl transferase required for the establishment of sister chromatid cohesion, was expressed in neuronal progenitors during their mid- and late S-phase. We inactivated Esco2 gene. The resulting mice showed severe cortical defects and cells derived from mutant were deficient in both, cell proliferation and DNA repair. The cellular basis of this defect will be discussed. The inability of Esco2-deficient cells to proliferate results in their demise through apoptosis, and makes them a target for tissue specific cell ablation using appropriate Cre driver lines. The potential of using Esco2 mutant mice for studying adult neurogenesis will be discussed.

Kanser Kök Hücreleri ve Beyin Tümörlerinin Epigenetik Regülasyonu

Epigenetic Regulation of Cancer Stem Cells and Brain Tumors

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Turk Norol Derg 2010;16(Ek 1):8-9

ÖZET

Kök hücreler, bulundukları canlıda bütün dokuları ve organları oluşturma potansiyeline sahip, sınırsız bölünebilen, kendilerini yenileyebilen, farklılaşmamış hücrelerdir. Kanser kök hücresi hipotezi, normal doku kök hücreleri ile tümör hücreleri arasındaki benzerlikleri ortaya koyar. Nadir ve yavaş bölünüyor olmaları nedeniyle, kök hücreleri kanser tedavisi için önemli bir sorun yaratmaktadır ve yeni terapi yaklaşımları kanser kök hücrelerinin niteliklerinin daha iyi ortaya konulması gerekliliğini göz önüne alarak gerçekleştirilmelidir. Kanser kök hücreleri ilk kez lösemilerde tanımlandığında, normal hematopoietik kök hücreleriyle yüzey proteinleri ve çoğalma şekilleri de dahil olmak üzere pek çok ortak özellikleri paylaştıkları gösterilmiştir. Son zamanlarda, merkezi sinir sistemi kök hücrelerine benzerlik gösteren hücreler, beyin tümörlerinden izole edilmiştir. Gliyoblastoma multiforme (GBM) kötü huylu gliyal tümörler arasında en yaygın olanıdır ve her ne kadar GBM etyolojisi ile ilişkili gen mutasyonları tanımlanmış olsa da, etkili bir tedavi henüz yoktur. GBM'de altta yatan moleküler mekanizmaları anlamak, daha etkili tedavi yaklaşımları geliştirmeyi sağlayacağından, kanser kök hücrelerinin epigenetik regülasyonunu karakterize etmek önemlidir. Epigenetik mekanizmalar, DNA metilasyonu, histon modifikasyonu ve mikroRNA aracılığıyla, gen ekspresyonunda kalıtsal değişiklikleri DNA dizisini değiştirmeden kontrol ederler. Epigenetik mekanizmalar çevresel sinyallerle genetik kodu birbirine bağlayıp, hem normal gelişmede hem de kanser dahil olmak üzere bir çok hastalığın etyolojisinde önemli rol oynarlar. Bu nedenle, epigenetik mekanizmaların GBM gelişimi ve ilerlemesindeki rolünü anlamak kanser kök hücrelerini hedef alan etkili tedavi yöntemleri geliştirmek için zorunludur.

ABSTRACT

Cancer stem cell hypothesis suggests the presence of similarities between the self-renewal of tissue stem cells and propagation of tumor cells. The slow proliferative characteristics and the quiescent state of the stem cells present an important problem for effective cancer treatment, and the future therapies must include the identification and characterization of these cells. Cancer stem cells were first characterized in leukemia, and they shared many properties of the hematopoietic stem cells (e.g., similar cell-surface marker expression, proliferation characteristics and progeny). Recently, cells with characteristics

of neural stem cells were isolated from human brain tumors. Among these, glioblastoma multiforme (GBM) is the most common and malignant form of the glial tumors. Although a number of gene mutations have been associated with the etiology of GBM, there is no effective treatment exists today. In order to better understand the underlying molecular mechanisms in GBM and to develop better therapeutic approaches, it is necessary to characterize the involvement of epigenetic mechanisms in the development and progression of GBMs with a specific focus on cancer stem cells. Epigenetic mechanisms refer to biological processes that regulate heritable changes in gene expression without altering the DNA sequence. Major epigenetic mechanisms include DNA cytosine methylation, histone modifications and small non-coding micro-RNAs. Epigenetic mechanisms link environmental signals and maintenance of genomic responses during development and have been implicated in number of disease conditions, including cancer. Therefore, it is crucial to understand how epigenetic mechanisms are involved in the development and progression of GBMs.

Bilişi Anlamada Davranıştan Biliş/Beyin Paradigmasına, Psikoloji Biliminden Nörobilime

Paradigm Change in Pursuit for Understanding Cognition: From Behavior to Cognition/Brain, From Psychology to Neuroscience

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ÖZET

İnsan zihnini anlama arzusu/gereksinimi her zaman var olmuş, bilim-öncesi psikolojide incelen nesne ruh ve daha sonra zihin olarak anılmış; bilim-sonrası psikolojide ise inceleme konuları, sırasıyla, bilinç (yapısalcı ve işlevselci ekoller), davranış (davranışcı ekol), bilinç-altı (psikoanalitik ekol) ve nihayet biliş (1950'ler ve sonrası) olmuştur. Ancak, tanımı ne olursa olsun psikolojinin bilgileri daima dıştan gözlenen davranışlar olmuş, bilişsel özellikler konusundaki bilgiler, standart koşullar dizisine verilen davranışlardan çıkarsama/tahmin yoluyla elde edilmiştir. Geçmişindeki bütün bu farklı görüş açıları psikolojinin zenginliğini oluşturmuş, biriken bilginin sağladığı güç, onu, meslekleri tercih sıralamasında en yukarılara getirmiştir. Ancak kullandığı "davranış paradigması", psikoloji bilimini, zihin/biliş/duyguları anlama konusunda bir sınıra getirmiş; daha fazla ilerleme, yeni bir paradigmayı kaçınılmaz kılmıştır.

Günümüzde biliş ve beynin ilişkili olduğu, temel ve uygulamalı bilim çalışmaları sonucunda, genelgeçer bilgi statüsünü kazanmıştır. Psikoloji biliminin yol haritasındaki bir sonraki durak da, davranış/bilişi beyine atıf yaparak ele almak bulunmaktadır. Esasen "biliş/beyin paradigması" sadece psikoloji biliminin değil, beyni veya bilişi inceleyen tüm bilim alanlarının sorunsalıdır. Zira, bu paradigmanın gerçek uygulama yeri, konuların bölüştürülmüş olduğu bilim alanları değil, disiplinler-arası ve hatta multidisipliner yaklaşımın kullanıldığı "nörobilim"dir.

Biliş/beyin paradigması altında; dakika, hatta saat/gün/yıl cinsinden ele alınan davranış/biliş, elektrofizyolojik eşlenikleri yoluyla, milisaniyeler düzeyinde incelenmektedir. Psikolojik süreçler sırasında oluşan elektrofizyolojik faaliyetin beynin hangi alanlardan kaynaklandığı, gelişmiş sinyal işleme teknikleri ile hesaplanabilmektedir. Fonksiyonel manyetik rezonans görüntüleme, psikolojik süreçler sırasında beynin hangi alanlarının çalıştığını yüksek mekansal çözünürlükle göstermektedir. Bütün bunların sonucunda, "davranışlardan, arada olup bitenleri tahmin etme" biçimindeki yaklaşım gerekli olmaktan çıkmakta; arada olup bitenler doğrudan gözlenebilmekte ve ölçülebilmektedir.

Anahtar Kelimeler: Biliş/beyin paradigması, multiteknolojik yaklaşım, psikoloji ekolleri.

ABSTRACT

Mankind always had the desire or felt the necessity to understand human cognition. From pre-scientific to scientific psychology, cognition was labeled as soul/spirit, mind, conscience (structuralism, functionalism), behavior (behaviorism), unconscious (psychoanalytic school), and finally cognition (from 1950's on). Psychology has always studied directly observable behavior; cognition was indirectly inferred from the directly observable behavior. The myriad of concepts and definitions of psychology have contributed to the richness of psychology. The utility of the accumulated psychological information have placed the branch within the realm of the most preferred professions. However currently, the marginal returns of the "behavioral paradigm" has become nearly nil, and further progress has made a paradigm change obligatory. The next station in the roadmap of psychology requires the treatment of cognition in reference to the brain. Actually, "cognition/brain paradigm" is critical not only for the science of psychology but for all other sciences that study cognitive processes. With this paradigm, cognition/behavior where temporal units start from minutes can be studied with high temporal resolution using neuroelectric responses, where units of measurement are milliseconds. Using neuroelectric activity and advanced techniques of signal analysis, brain sources of the activity and thus of the cognitive processes can be calculated. Functional magnetic resonance imaging can show, with unsurpassed spatial resolution, brain areas that accompany cognitive processes. This multitechnological approach bypasses inferential processes ("what happened inside the black box is inferred from directly observable behavior") and makes it possible to directly observe and measure the intervening cognitive processes on the basis of brain processes.

Key Words: Cognition/brain paradigm, multitechnological approach, historical schools of psychology.

The Mirror Neuron System as a Neural Basis for a Non Verbal, Gesture Mode of Communication

Dil Ötesi İletişimin Temelindeki Ayna Nöron Sistemi

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ABSTRACT

The discovery by Giacomo Rizzolatti and co-workers (including Luciano Fadiga, head of Serâ Tokay's empirical research) of 'mirror neurons' in a frontal area of monkey brain, the homologue of Broca in man, revived the motor origin of language hypothesis, an hypothesis that remains yet controversial. On the other hand, robust empirical data came to back up the existence of correlates in motor circuits for non verbal, gestural, aspects of human communication. When an agent happens to be focus of attention of an observer whose motor memory includes the observed actions, a direct link automatically sets up between both. The cortical motor maps of their brains set about resonating as a result of the impact of the scene on the observer's motor system in conjunction with an inhibition of its bodily movements. Amounting to an internal simulation, such resonance might enable the observer anticipating the other's actions. A gesture mode of communication contingent upon maximally extending the human resources in action anticipation, the art of conducting clearly lends itself to an investigation along the lines of the mirror system paradigm. In the wake of the literature on internal models and statistical inference a driving force criterion was successfully applied comparing the performances of two conductors and the coordination of musicians under their direction, thereby paving the way to a future science of conducting.

Key Words: Motor system, mirror neurons, action understanding, anticipation, simulation, gesture, driving force.

Empathy Between Conductor and Orchestra: Phenomenology and Empirical Research

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ABSTRACT

We are trying to come to terms with certain phenomenological intuitions, born of the practice of orchestral conducting, in a manner as free as possible of technical jargon. The articulation of these intuitions has been integrated within a program of research developed by Prof. Luciano Fadiga. A first stage in the development of this program has already taken place in Istanbul, with a session dedicated to the recording of stringed instruments. Our central intuition: contrary to the dogma of a quite naive though well represented dogma in musicological literature, conducting an orchestra does not consist, first and foremost, in the conductor enjoying some kind of privileged access (direct or not) to the musical representations of the instrumentalists – and vice versa. Conducting an orchestra is much more a matter of the conductor possessing a (non representational) kinesthetic capacity to reproduce, in depth, the style of his or her own lived experiences, so that they become a sort of analog of the expert gestures of the instrumentalist. A transfiguration whose paradoxical radicality goes as far as reinventing the breathing process, the latter being subject to the ordinary physiological necessities that follow from having to raise and lower the arms with each phrase in the execution of the musical work. Without the conductor having to say a word, his or her baton - according to the classical phenomenological description of the instrument, a prolongation of the entire body (and not simply of the anatomical hand) - affectively takes account of all the distortions imposed upon this body by the incarnation of the musical ideality of the work. This analysis, apparently concentrated upon the kinesthetic sensations of the particular individual who happens to be the conductor also tells us a great deal about empathy. In the immanental auto-affection of a re-configured corporeal experience, the task of incarnating through gestures the musical meaning of the work interpreted by the conductor is uniquely orientated around the possible resonances of his or her gestures with the gestures productive of the sound of each instrumentalist, singly and individually. A great conductor is inter-subjectively engaged, right down to his or her corporeal gestures.

Getting to Treatments for Brain Diseases: New Partnerships

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ABSTRACT

The history of drug development to date may be considered as occurring in 4 eras. First there was the Age of the Plant, when individuals experimented opportunistically with plant medicines. Second, the Age of the Apothecary, when useful natural agents as well as knowledge about their use was systematically collected and stored in shops that sometimes also sold perfumes or spices. Third, in the 19th century, the Age of Synthesis when the pharmaceutical industry emerged from the synthetic dye industry; new molecules with synthesized based on coal tar distillates, formulated into tablets and capsules and produced on an increasing scale. Fourth, beginning systematically only in 1966, was the Age of Proven Value, when the US Food and Drug Agency (FDA) contracted with the National Academy of Sciences to examine the evidence supporting the efficacy of marketed drugs, and scientific proof of efficacy became required for regulatory approval. Subsequently, beginning in the 1980s, pharmaceutical companies exponentially increased investment in drug research and development, believing that biomedical science had advanced sufficiently to usher in a fifth era: the Age of Design, when purposefully-created therapeutic drugs would routinely meet expectations.

Unfortunately, despite this marked increase in research and development, now exceeding $50 BB across the worldwide pharmaceutical and biotechnology industries, the productivity of industry pipelines has been disappointing. Pipeline performance has sagged back from the peak performance reached in the 1990s, in recent years delivering less than 30 new active substances registered annually. Perhaps this global pipeline failure is in part due to premature dependence on Age of Design-based "forward drug discovery"?

Drawing in part on my personal experiences as a researcher in the field of excitotoxicity and neuroprotection, as well as work in the pharmaceutical industry, I have come to the view that we are unfortunately not yet truly in the Age of Design. To improve pipeline performance, it may be desirable to return temporarily to a greater emphasis on drug screening and broad explorations of drug effects in early clinical testing, certainly guided by all the data and scientific tools at our disposal, but more humbly recognizing that there is much we still do not know about complex biological systems. Accomplishing this retro shift would be facilitated by the development of new partnerships amongst industry, academia, government, and private disease foundations.

Pharmacological and Physiological Control of 5-HT Neurons

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Turk Norol Derg 2010;16(Ek 1):15

ABSTRACT

The neurotransmitter 5-hydroxytryptamine (5-HT, serotonin) mediates important brain functions and contributes to the pathophysiology and successful drug treatment of many common psychiatric disorders. A key mechanism involved in the control of 5-HT neurones is feedback inhibition by presynaptic 5-HT autoreceptors, located on 5-HT cell bodies and nerve terminals. In addition, recent experiments have found unexpected complexity in 5-HT neurone control, specifically in the form of postsynaptic 5-HT feedback mechanisms. These mechanisms have the inhibitory effects of 5-HT autoreceptors but use additional 5-HT receptor subtypes, and operate via neural inputs to 5-HT neurones. A postsynaptic feedback system that excites 5-HT neurones has also been reported. This presentation will focus on recent discoveries of the pharmacology and physiology of 5-HT feedback mechanisms, based on approaches ranging from neuropharmacological investigation through to genetic manipulation and neuroimaging. The presentation will include an assessment of both the likely contribution of these mechanisms to psychopathophysiology and future psychotropic drug discovery, and the scope for modelling these mechanisms using experimental approaches that translate from animals to man.

Oxytocin: Healing Body, Brain and Behavior

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ABSTRACT

Oxytocin is an ancient neuropeptide hormone, best known for its role in birth and lactation. This presentation will describe new research suggesting that oxytocin is neuroprotective, with healing effects throughout the body. Many of the effects of oxytocin appear positive, since high levels of oxytocin or treatments with exogenous oxytocin are associated with reductions in stress reactivity, faster wound healing and reductions in psychiatric symptoms associated with autism, schizophrenia, anxiety and depression. A model for the behavioral, autonomic and emotional effects of oxytocin will be presented, including concerns regarding the possible overuse or abuse of this molecule.

Neurobiological Perspectives on "Love" and Social Bonding

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Turk Norol Derg 2010;16(Ek 1):17

ABSTRACT

Historically the concept of "love" was considered primarily relevant to humans and perhaps the domain of poets and artists (Carter, Psychoneuroendocrinology, 1998). However, at the heart of love are social behaviors and social bonds that also can be studied in other species including social monogamous rodents, such as prairie voles. Based on the natural history of voles and by moving this species into the laboratory we were able to demonstrate roles for several neuropeptides (oxytocin, vasopressin, and CRF) in various forms of sociality including the formation of social bonds. In addition, neonatal experiences and exposure to neuropeptides in early life can "tune" the nervous system with behavioral and endocrine consequences that last throughout the life-span. These findings allow us to examine the neurobiology of love and other forms of selective social behavior with results that have implications for understanding both mental health and mental illness.

Mechanisms of Electromagnetic Field (EMF) Effects on the Brain

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Turk Norol Derg 2010;16(Ek 1):18

ABSTRACT

Epidemiology studies show an increased risk of brain tumors associated with exposure to EMF from mobile phones. Laboratory studies show that EMF can cause DNA strand breaks and lead to mutations that cause cancer. EMF can also cause leakage of the blood brain barrier and lead to death of brain cells. The biological effects of power frequency and radiofrequency EMF, including stimulation of electron transfer and stress protein synthesis, support the idea that changes in DNA caused by EMF are a plausible molecular mechanism that can account for the observed increased risk of cancer. EMF stimulation of the Cellular Stress Response, a protective cellular reaction to potentially harmful stimuli such as high temperature and acidity, shows that cells react to EMF as potentially harmful. Since many of biological responses to EMF (including interaction with DNA) occur well below the specific absorption rate (SAR) level that is considered safe, the public is not protected from exposure to EMF from mobile phones, mobile phone masts, WiFi systems, etc. It is therefore important that the public be made aware of the potential dangers of EMF exposure and encouraged to take precautionary measures.

Key Words: Electromagnetic fields (EMF), cellular stress response, DNA strand breaks, brain tumors, blood brain barrier.

The Action Potential as A Propagating Mechanical Pulse, the Action of Anesthetics and Lipid Channel Formation

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Turk Norol Derg 2010;16(Ek 1):19

ABSTRACT

Biological membranes display melting transitions close to physiological temperatures. This feature leads to the possibility of density pulse (soliton) propagation in such membranes. We discuss the propagating pulses in the context of several striking properties of nerve membranes under the influence of nerve pulses, including mechanical dislocations, temperature changes and the formation of lipid ion channels. The appearance of quantized currents is a thermodynamic necessity under conditions where solitons propagate, and do not require the direct involvement of proteins. We relate pulse propagation to the famous but so far unexplained Meyer-Overton rule stating that the effectiveness of an anesthetic is proportional to its membrane solubility. Anesthesia may find an explanation in the well-known general phenomenon of freezing point depression.

The Nobel Prizes in the Field of Neuroscience. From Camillo Golgi and Ramón y Cajal to Richard Axel and Linda Buck

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ABSTRACT

Sixteen Nobel Prizes have been awarded the field of neuroscience, the first one in 1906 to Camillo Golgi and Ramón y Cajal and the last one so far in 2004 to Richard Axel and Linda Buck. This presentation will give a brief survey over the contributions by the different laureates. Special emphasis will be put on contributions by some early Prize winners who have been pioneers in the field like Golgi and Cajal and Sherrington and Adrian, as well as Erlanger and Gasser. For these laureates the speaker has had the possibility to penetrate the original documents at the Nobel Archives at Karolinska Institutet. Information about the remaining laureates has been collected from the website www.nobelprize.org, which has now an impressive amount of information, including the Nobel lectures given by the laureates.

The Logic of Networks in Motion-From Ion Channels to Behaviour

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ABSTRACT

To unravel the intrinsic function of the networks controlling vertebrate motor behaviour, we have developed a lower vertebrate model system, the lamprey. In this system it has been possible not only to unravel the intrinsic function of the pattern generating network and the command system by which it is activated, but also the control systems underlying steering and the control of body orientation during movements. The lamprey nervous system has fewer neurones, and the motor pattern underlying the locomotor behaviour can be elicited in the isolated nervous system. The pattern generating network contains ipsilateral glutamatergic interneurones and crossed inhibitory glycinergic interneurones. The synaptic interaction, membrane properties and transmitters in the network have been identified. It is activated from the brainstem reticulospinal neurones, which in turn are controlled from diencephalon and mesencephalon with separate populations of locomotor command neurones. The locomotor behaviour can thus be turned on from these two 'locomotor centres'. These two areas are in turn under the control from the basal ganglia, which play a main role for selection of which motor program is turned on at a given instant. The output nuclei of the basal ganglia provide tonic inhibition under resting conditions to different motor centres, and elicit activation of a centre through disinhibition. Striatum and pallidum are viewed as critical structures for the selection of a given motor program.

We have developed detailed network models based on Hodgkin-Huxley model neurons of each cell type with appropriate sodium, potassium, calcium ion channel subtypes and also calcium dependent potassium channels. Each model neuron has up to 86 compartments and behaves as its biological counterpart, with regard to frequency regulation, afterhyperpolarization and so forth. The different network models neurons are then connected synaptically as established experimentally. The 10.000 model neurons correspond to the approximate number in the biological network. The number of synapses is 760.000. Synapses are of AMPA, NMDA and glycine type. With this large scale modelling, we can simulate not only the segmental and intersegmental coordination but also the initiation of behaviour from the basal ganglia. Moreover, these networks have also been used in a neuromechanical model simulating actual locomotion with propulsion and steering.

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From Cold to Pain: Molecular and Cellular Mechanisms

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ABSTRACT

Cold temperature can evoke a wide spectrum of perceptual sensations that range from freshness to unpleasant cold or overt pain. In mammals, the detection of cold temperature is accomplished by the activation of different subsets of sensory terminals innervating the skin and mucosae. Direct recordings of cold nerve endings, combined with studies of thermoreceptive neurons in culture, have allowed the characterization of ionic mechanisms involved in cold temperature sensing. Cell bodies of cold-sensitive neurons exhibit characteristic active and passive membrane properties and are equipped with a number of specific ionic conductances (TRPM8 and background K+ currents, TRPA1, IKD and Ih) that are variably expressed in the soma and peripheral endings of primary sensory neurons and determine the thermal threshold and firing characteristics of their peripheral sensory endings. We analyzed the gating by cold of specific ion channels and its relationship with the activation of particular sets of afferent fibers and concluded that cold thermotransduction is complex and involves the concerted operation of several ion channels. Excitatory effects of cationic channels (e.g.,TRPs) balance their activity with several excitability brakes (e.g., potassium channels), leading to tunable levels of sensory thresholds and activity. Sensations of freshness and innocuous cooling are mediated by low threshold cold-sensitive neurons whereas the population of high threshold cold neurons possibly mediates sensations of unpleasant cold. Injury alters thermal responsiveness of cold-sensitive neurons and may lead to thermal dysesthesias. In addition to their contribution to conscious thermal sensations and thermoregulatory responses, cold termoreceptors may participate in other functions, such as detection of air flow in the respiratory pathways, blood flow changes in ocular vessels and measurement of humidity levels in superficial mucosae.

Neuron-Glia Metabolic Coupling

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ABSTRACT

Over the last few years our laboratory has described the cellular and molecular mechanisms that underlie the coupling between synaptic activity and glucose utilization by the brain. We have identified a central role of astrocytes in these mechanisms. Glutamate is sensed by astrocytes through its transporters; this uptake triggers glucose uptake which is processed glycolytically providing lactate as an energy substrate for neurons. Evidence from other laboratories has indicated that astrocytes also play a key role in coupling synaptic activity to vascular responses. Thus astrocytes can be viewed as central elements in coupling synaptic activity to energy delivery to the activated brain areas. These mechanisms also provide a basis for functional brain imaging techniques to visualize brain activity such as fMRI and PET.

Reperfusion Injury to Neurovascular Unit and No-Reflow Phenomenon

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ABSTRACT

The neurovascular unit, composed of the endothelium, astrocytes, pericytes, smooth muscle cells, proteins and enzymes in the extracellular matrix, is a major target of ischemia/reperfusion-induced injury. We previously showed that, during ischemia/reperfusion, oxidative-nitrative stress on the microvascular wall is intense and may cause opening of the blood-brain barrier (BBB) by activating matrix metalloproteinases and, hence, contribute to brain edema and hemorrhage seen after reperfusion.

Pericytes have a key role in regulation of capillary blood flow by contracting and dilating with various chemical stimuli originating from neighboring astrocytes and neurons. We have recently found that pericytes on microvessels contract during ischemia and remain contracted after reopening of the occluded artery. Erythrocytes are trapped at the capillary constrictions and obstruct microcirculation. Suppressing oxidative-nitrative stress alleviates ischemia/reperfusion-induced pericyte contraction and improves capillary reflow. These new findings point to a previously unrecognized mechanism; ischemia-induced injury to pericytes may impair microcirculatory reflow and negatively impact survival by limiting oxygen delivery to tissue under metabolic stress, despite recanalization of an occluded artery.

We conclude that agents that can suppress oxidative-nitrative stress to the neurovascular unit may increase the success of thrombolytic and neuroprotective treatments by reducing BBB disruption and restoring microvascular patency after recanalization therapies.

An In Vivo Gene Knockdown Approach for Functional Assessment of Dopaminergic Input to the Striatum

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ABSTRACT

The functional significance of the dopamine input to the striatum has been established by catecholamine-specific neurotoxin lesion models where the pre-synaptic nerve terminals are damaged and degenerate to gradually lead to cell death in the ventral midbrain where the cell bodies are located. While this approach has been very powerful in elucidating motor and cognitive symptoms related to dopamine depletion and restorative therapies that aim to re-construct the lost dopamine input to the striatum, it did not provide a suitable model to dissect the pathogenetic mechanisms for induction and maintenance of abnormal involuntary movements (dyskinesias), a commonly encountered side effect of L-DOPA medication. We have taken advantage of the short hairpin RNA's as a means to knockdown the expression of the tyrosine hydroxylase (shTH), and therefore silenced the dopaminergic cells without structurally damaging them. Using genetic tools and pharmacological activation studies, we were able to provide direct evidence that the activity of the pre-synaptic compartment is a critical determinant of both the induction and maintenance of L-DOPA-induced dyskinesias in rats.

Strategies for Peripheral Nerve's Tissue Engineering

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ABSTRACT

Recently much interest has been dedicated to the perspective of improving peripheral nerve repair and regeneration by means of tissue engineering and, similarly to many other fields of regenerative medicine, great expectations have risen within the general public to its potential clinical application in the treatment of damaged nerves. However, in spite of the scientific advancements, applications to the patients is still very limited and it appears that to optimize the strategy for the tissue engineering of the peripheral nerves in the clinical view, more basic science research is needed and neuroscientists have to strive for a new level of innovation which will bring together (in a multi-translational approach) the main pillars of tissue engineering, namely 1) Microsurgery, 2) Transplantation (of tissues, cells and genes), 3) Material science, 4) Physical therapy. In this presentation, I will provide an brief overview of these four key approaches to peripheral nerve tissue engineering in order to throw a light on the most promising future perspectives in combining the different strategies for improving posttraumatic recovery. In particular, I will focus on an example of successful translational research in tissue engineering, namely nerve reconstruction by muscle-vein-combined nerve scaffolds, on which we have carried out a series of experimental and clinical studies over the last fifteen years, as well as on some of the pitfalls which may arise in this research field.

Axotomy-induced Neuronal Plasticity and Regeneration in the Peripheral Nervous System

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ABSTRACT

Peripheral nerve lesions cause motor and sensory deficits with often serious clinical consequences such as prolonged paralysis, anaesthesia and neuropathic pain. Therefore, improvement of long-distance axon growth is required for fast regeneration of axons into target muscles which atrophy in the absence of reinnervation.

Primary neurons derived from dorsal root ganglia are particularly suitable to study regeneration-associated neuronal plasticity. Their axons rapidly regenerate after lesion because of the permissive environment provided by Schwann cells, extracellular matrix and neurotrophic activities in vivo. Various families of neurotrophic factors exist, for example, the neurotrophins and members of the fibroblast growth factor (FGF) family.

Some of the different FGF proteins and their receptors play a prominent role in axon growth during brain development and axon regeneration in the adult nervous system. FGF-2 (basic fibroblast growth factor) is up-regulated in response to nerve injury and has been shown to promote neuronal survival and neurite outgrowth. FGFs mediate their response by activation of four types of high affinity tyrosine kinase receptors (FGFR1-4). Novel negative feedback regulators of FGFR signaling have been described, but their significance for axon growth has not been investigated so far.

Our laboratory (www.neuroanatomy.at) focuses on the signaling pathways activated by FGFR1 to influence different modes of regeneration, such as axon elongation, branching and maintenance. FGFR1 overexpression and inhibition of receptor degradation strongly stimulate the neuronal ERK pathway and promote elongative axon growth by adult sensory neurons. Degradation of FGFR1 can be inhibited by the lysosomal inhibitor leupeptin and by the proteasomal inhibitor lactacystin. FGFR1 overexpression enhances FGF-2-induced axon growth by sensory neurons, which is further increased by co-treatment with leupeptin. Therefore, lysosomal inhibition of receptor degradation concomitant with ligand stimulation of neurons overexpressing FGFR1 represents a new mechanism of tyrosine kinase receptor mediated promotion of axon regeneration, and demonstrates that adult sensory neurons express sub-optimal levels of tyrosine kinase receptors for neurotrophic factors.

Furthermore, Sprouty proteins act as negative feedback inhibitors of the ERK pathway. Down-regulation of Sprouty2 via transfection of shRNA promotes elongative axon growth by peripheral and central primary neurons. In response to Sprouty2 knockdown, enhanced FGF-2-induced activation of ERK and Ras is observed, but phosphorylation of Akt and p38 remains unaffected. Our results imply that Sprouty2 is highly expressed in adult peripheral neurons and its down-regulation strongly promotes elongative axon growth by activation of the Ras/Raf/ERK pathway suggesting novel novel therapeutic strategies to promote rapid and specific peripheral axon elongation in vivo (supported by FWF, MUI, COST B30).

Can Brain Research Help Our Society?

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ABSTRACT

Since the beginnings of culture, human beings have been trying to understand the biological world and more precisely, their own human nature. The brain possibly represents the last frontier and the main challenge in the adventure of exploring the unsolved mysteries of modern biology. In recent decades, the study of the nervous system has experienced revolutionary advances in different fields, extending from the molecular and cellular basis of neuronal function and connectivity, to the genetic, molecular and cellular processes governing brain development or how brain circuits are organized to develop its astonishing functions. This new knowledge is permitting a better understanding of nervous system pathologies and opens promising ways for their treatment. But perhaps more importantly, brain research is changing our views on the biological constrains of human behavior and is shading new light on controversial questions such as the biological limits of human freedom, the basis of violence, sex differences in behaviour or children's learning, to cite only a few examples. Advances in brain research will hopefully help modern societies to develop rules, values and behaviors better adapted to the biological realities of the human brain.