The Neuron Doctrine: Was it Just The Cell Theory Applied to Nervous Tissue or Did its Power Have Another Source?

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ABSTRACT

The neuron doctrine, formally expressed by Waldeyer, fiercely attacked by Golgi and defended by Cajal, was and continues to be a powerful tool for neuroscientists. Although it has been described as "one of the great ideas of modern thought, comparable to the quantum theory, relativity, the cell theory, or the theory of evolution" (Shepherd, 1991), Bullock et al. Wrote in Science in 2005: "The doctrine... no longer encompasses important aspects of neuron function." and "Information processing in the nervous system must operate beyond the limits of the neuron doctrine ...."

This lecture will explore some of the historical background for understanding what the neuron doctrine claimed and why it was attacked by Golgi and other "reticularists". I will consider where the neuron doctrine has been a powerful conceptual tool for neuroscientists, how it relates to the cell theory and where modern knowledge about the nervous system is contrary to one or another aspect of the doctrine. I shall argue that we still need the neuron doctrine and that it is may be important to teach our students about its strengths and its weaknesses.

Key Words: Neuronist, reticularist.

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Brain Clocks, Inflammation and Ageing

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ABSTRACT

Life flows over time, the fourth dimension of life, which shapes our days, months and years and clocks tick in the brain to measure time. In mammals, biological rhythms are controlled by the suprachiasmatic nuclei (SCN) of the anterior hypothalamus which function as a master biological clock. The SCN thus governs the sleep-wake cycle, as well as of endogenous rhythms in behavioral, hormonal and immune functions. Other neural cell groups act as "switches" of biological functions. For example, orexin-containing neurons in the dorsolateral hypothalamus play a key role in wake regulation and are involved in circuits underlying the transition from sleep to wake. Despite the wealth of knowledge accumulated in the last years on the regulation of the SCN and brain "switches", the effect exerted by inflammatory signalling on these cell groups has been relatively neglected, though it can be implicated in diverse pathological and physiological conditions. Paradigmatic is, in this context, a severe neuroinflammatory condition represented by African trypanosomiasis or sleeping sickness. This neglected parasitic disease, which is fatal if uncured, is hallmarked in humans by alterations of the sleep-wake cycle. Findings which implicate a dysregulation of brain clock/s in experimental models of this disease will be discussed. On the other hand, in the context of physiological conditions, a number of data in the last years have pointed out that normal aging is hallmarked by low-grade chronic inflammatory activity, with increased production of proinflammatory cytokines peripherally and in the brain and decreased anti-inflammatory mediators. A puzzling aspect of aging is represented by the frequent dysregulation of endogenous biological rhythms, and especially of the sleep/wake cycle, and data will be presented on aging-related changes of brain clock/s. The talk will thus delineate an itinerary of research focusing on neural-immune interactions in the brain timing machinery.

Key Words: Suprachiasmatic nucleus, sleep, neuroinflammation.

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Why William of Ockham is Not a Good Guide to Dementias

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ABSTRACT

One of the most fundamental questions in modern neuroscience in general and in dementia research in particular is the relationship between the clinical phenotypes of neurological diseases, as observed by the medical practitioners, and the underlying pathological changes, as revealed by the basic scientists. Under the influence of the principle of parsimony, often referred to as "Ockham's razor", the predominant tendency for many decades has been to assume that a specific clinical picture must ultimately be caused by a specific pathology et vice versa. However, our increasing knowledge of the more subtle aspects of dementia as well as the enormous progress in basic sciences over the last decade has led to a much more complex picture, with multiple and not always straightforward correspondences between the phenotype and the pathology. In my talk I will try to interpret this apparent chaos, focusing in particular on the relationship between language, movement and cognition.

Key Words: Clinico-pathological studies, dementia, neurodegeneration.

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The Functional Organisation of the Basal Ganglia

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ABSTRACT

The basal ganglia are a group of subcortical nuclei that are involved in a variety of functions including motor, cognitive and mnemonic behaviours. Central to basal ganglia function is the relationship between the glutamatergic projection from the cortex to the striatum, and the dopaminergic innervation of the same region from the substantia nigra. Thus excitatory corticostriatal afferents mainly innervate the spines of medium-sized spiny neurons (MSNs) that in turn give rise to the direct and indirect projections to basal ganglia output nuclei. The response of MSNs to the cortical input is modulated by the release of dopamine at the neck of the spine. The mechanisms underlying the modulatory role of dopamine are numerous and dependent on a variety of factors including the type of dopamine receptor and the activity of dopaminergic neurons, but the net outcome is a facilitation or attenuation of the excitatory transmission (1). The striatum also receives a major glutamatergic projection from the intralaminar thalamic nuclei that is of similar magnitude to the corticostriatal input (2). Extracellular recording and juxtacellular labelling revealed that thalamostriatal neurons in the central lateral and parafascicular nuclei have distinct electrophysiological and morphological properties (3). Double-immunolabelling to reveal vesicular glutamate transporters 1 or 2 as markers of cortical and thalamic terminals respectively, and tyrosine hydroxylase to label the dopaminergic axons, has revealed similar relationships between thalamic and dopaminergic terminals and cortical and dopaminergic terminals (4). Furthermore, similarly-sized structures within the striatum are equally likely to be apposed by a dopaminergic axon. Thus the input from the thalamus underlies a rich and diverse complexity of function on a par with that of the corticostriatal projection. Thalamostriatal and corticostriatal terminals are equally likely to be influenced by released dopamine and that the nigrostriatal projection is organised in such a way that every striatal structure has the potential to be influenced by dopamine.

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Key Words: Corticostriatal, thalamostriatal, dopamine.

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Spinothalamic Neurons and Sexual Dimorphism

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ABSTRACT

As the name indicates, spinothalamic tract (STT) neurons send sensory information that comes into the spinal cord to the thalamus; from there the sensory information is sent to various cortical regions. Recent studies have shown that the number of STT neurons in laminae VII and X of spinal segments L1-5 is sexually dimorphic with males having a larger number of these lumbar STT neurons than females. These lumbar STT neurons are situated among the L1,2 preganglionic sympathetic neurons and extend to the L5 preganglionic parasympathetic neurons. This population of laminae VII and X lumbar STT neurons co-contain the neuropeptides galanin (GAL) and cholecystokinin-8 (CCK-8) which are involved in processing nociceptive information. Studies show that the qualitative amounts of these two peptides are sexually dimorphic (male > female) and controlled by androgen titers; male rats with non-functional androgen receptors (testicular feminization mutation) have qualitative levels of GAL and CCK-8 that are female-like. This sexual dimorphism, which is part of a spinal-supraspinal-spinal sexually dimorphic pain circuit, may provide an anatomical basis for the sex differences in the affective and motivational component of somatic and visceral pain perception in pelvic diseases such as cystitis and irritable bowel syndrome. The presence of these lumbar STT neurons among the spinal autonomic neurons suggests that they may contribute to the sexually dimorphic functions of the autonomic nervous system to the pelvis.

Key Words: Spinothalamic neurons, Sexual dimorphism, Nociception.

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Cinsel İstek ve Sertleşme İşlev Bozukluğu

Sexual Arousal and Erectile Dysfunction

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ÖZET

Cinsel uyarılma ve istek cinsel ilişkinin önemli bir bölümünü oluşturan hazırlık dönemi olup, bir seri fizyolojik ve davranışsal değişikliği içerir. Cinsel uyarılma sırasında oluşan fizyolojik yanıtların birçoğu iyi bilinmektedir. Örneğin; kardiyovasküler, solunum ve cinsel bölge yanıtları, endokrin ve bağışıklık sistemi değişiklikleri gibi. Cinsel uyarı korteksin aktivitesinde de değişikliklere yol açar. Sesli-görsel cinsel uyarı bazı bölgelerde serebral kan dolaşımını artırır. Vücut kas sisteminde penis sertleşmesi ve pelvik taban kasları kontraksiyonu dışında diğer kasların cinsel uyarı sırasında nasıl etkilendiği fazla bilinmemektedir. Kavrama gücü üst ekstremitenin kas gücünü ölçmede klinik olarak kullanılan güvenilir bir yöntemdir. Bu yöntem cinsel uyarılmanın motor sistemini nasıl etkilediğini belirlemede kullanılabilir (1).

Diğer yandan, dokunma duyusunun cinsel uyarılmaya katkıda bulunduğu önerilmiştir. Dolayısıyla, dokunma ve vibrasyon duyularında oluşan değişiklikler cinsel fonksiyonu etkileyen faktörlerden biri olabilir. Penisin ve genital bölgenin cinsel uyarılma sırasında oluşan dokunma duyusu değişikliklerini araştıran bazı çalışmalar yapılmış olmakla birlikte diğer bölgelerde bu duyuların nasıl etkilendiği iyi bilinmemektedir. Ancak parmak ucunun vibrasyon algılama eşiği ölçümleri cinsel uyarılma sırasında önemli değişiklikler olduğunu göstermiştir (2).

Sertleşme işlev bozukluğu önemli ve yaygın bir tıbbi sorun olup, yeterli bir cinsel ilişkiyi oluşturacak düzeyde sertleşme olmaması veya devam ettirilememesi olarak tanımlanır. Bu sorun ileri yaşlarda daha sık görülse bile yaşlılığın kaçınılmaz bir sonucu değildir. Sertleşme işlev bozukluğu genelde organik ve psikolojik olmak üzere iki kategoriye ayrılır ve birçok tıbbi durumda görülür. Yapılan bir seri çalışma sonucunda organik olmayan sertleşme işlev bozukluğu hastalarının kavrama gücü ve vibrasyon algılama eşiği ölçümlerinden elde edilen sonuçların sertleşme sorunu olmayan sağlıklı kişilerden farklı olduğu saptanmıştır (3).

Anahtar Kelimeler: Cinsel istek, sertleşme işlev bozukluğu.

ABSTRACT

Sexual arousal is an important part of sexual activity and is a particular state of readiness, characterized by a series of adaptive physiological and behavioral changes. Many physiological responses to sexual arousal have been well-documented, e.g. cardiovascular, respiratory and genital responses, changes in endocrine and immune systems. Sexual arousal also results in changes in cortical activity. Cerebral blood flow increases in various regions in response to audio-visual erotic stimulation. However, little is known on muscular responses to sexual arousal, although some musculatures have been found to join and facilitate sexual activity, such as penile erection and the pelvic floor contraction during sexual arousal. Grip strength is a reliable and valid method of measuring upper limb muscle strength in clinical and physical procedures. This method could be used to determine the influences of sexual arousal on the motor system (1).

On the other hand, it has been proposed that tactile sensation contributes to sexual arousal. Consequently, changes in tactile and vibration sensitivity may be a factor that influences sexual function. A number of studies have investigated the changes in penile and genital tactile sensation during sexual arousal, but the effects on non-genital areas have not been well-documented. However, vibration detection threshold measurements at the fingertip reveal significant alterations during sexual arousal (2).

Erectile dysfunction (ED) is an important and common medical problem and is defined as the inability to achieve and/or maintain an erection sufficient for satisfactory sexual performance or intercourse. Although the incidence of ED increases with age, it is not an inevitable consequence of the aging process. ED can be generally classified into two categories; organic and psychological (non-organic), and is the result of many conditions. The results of grip strength and vibration detection threshold measurements obtained from patients with non-organic ED during sexual arousal have been shown to be different to results obtained from individuals without ED (3).

Key Words: Sexual arousal, erectile dysfunction.

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Monitoring Epileptogenesis with Novel Imaging Techniques: How Far is Lab Bench from Bedside?

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ABSTRACT

Development of temporal lobe epilepsy (TLE) can be triggered by various brain insults, including traumatic brain injury, stroke, or status epilepticus. Injury is followed by a latency phase (i.e., epileptogenesis), and finally, appearance of spontaneous seizures (i.e., epilepsy). During epileptogenesis, brain tissue undergoes remodeling, including neurodegeneration, gliosis, axonal injury and sprouting, vascular damage and angiogenesis, and degradation of extracellular matrix which can be monitored in vivo by MR imaging. This has provided an opportunity to search surrogate markers that would predict structural and functional outcome after brain injury in clinically relevant experimental models. Here we summarize our recent data that has focused on understanding how the severity of axonal rearrangements in the hippocampal circuits monitored with Mn-enhanced MRI, DWI, or DTI associate with risk of epilepsy in rat models of TLE. The data obtained will be discussed in context of human data available, and how to facilitate translation of experimental findings to clinic.

Key Words: Epileptogenesis, status epilepticus, surrogate marker, traumatic brain injury.

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Targeted Gene Deletion Reveals That PACAP is an Intrinsic Regulator of Treg Abundance in Mice and Plays a Protective Role in Experimental Autoimmune Encephalomyelitis

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ABSTRACT

Pituitary adenylyl cyclase-activating polypeptide (PACAP) is a widely-expressed neuropeptide that closely resembles vasoactive intestinal peptide (VIP), a neuropeptide well known to inhibit macrophage activity, promote Th2-type responses, and enhance regulatory T cell (Treg) production. Administration of PACAP, like VIP, has been shown to attenuate dramatically the clinical and pathological features of murine models of autoimmune diseases such as experimental autoimmune encephalomyelitis (EAE) and collagen-induced arthritis. However, specific roles (if any) of endogenous VIP and PACAP in the protection against autoimmune diseases have not been explored. Here, we subjected PACAP-deficient (KO) mice to myelin oligodendrocyte glycoprotein (MOG_{35-55})-induced EAE. MOG immunization of PACAP KO mice resulted in heightened clinical and pathological manifestations of EAE compared to wild type mice. The increased sensitivity was accompanied by enhanced mRNA expression of proinflammatory cytokines (TNF-α, IL-6, IFN-γ, IL-12p35, IL-23p19 and IL-17), chemokines (MCP-1/CCL2, MIP-1α/CCL3, and RANTES/CCL5) and chemotactic factor receptors (CCR1, CCR2 and CCR5), but down-regulation of the anti-inflammatory cytokines (IL-4, IL-10 and TGF-β) in the spinal cord. Moreover, the abundance of $CD4^+$ $CD25^+$ $FoxP3^+$ Tregs in lymph nodes and levels of FoxP3 mRNA in the spinal cord were also reduced. The reduction in Tregs was associated with enhanced proliferation and decreased TGF-β secretion in lymph node cultures stimulated with MOG. To examined potential cellular sources of TGF-β, we FACS-sorted MOG-induced lymph node cultures from immunized and non-immunized WT and PACAP KO mice by real time RT-PCR. In WT mice, MOG immunization resulted in an induction in TGF-β gene expression in macrophages ($CD11b^+$), dendritic cells ($CD11c^+$) and Th cells ($CD4^+$). However, the up-regulation in $CD4^+$ and $CD11c^+$ cells was completely blocked in PACAP KO mice. These results demonstrate that endogenous PACAP provides protection in EAE, and identify PACAP as an intrinsic regulator of Treg abundance after inflammation.

Key Words: Multiple sclerosis, PACAP, VIP.

Ölçüm Sonuçlarının Doğru ve Anlamlı Rakamlarla İfade Edilmesinde Uyulacak Kurallar

Rulers in Reporting of Measurement Results with Accurate and Significant Figures

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ÖZET

İdeal dünyada, ölçümler her zaman mükemmeldir. Bütün ölçümler kesin değerlere sahiptir ve bu nedenle bu ölçümlerle yapılan hesaplamalar da basittir. Ne yazık ki, deneyler ideal dünyada değil de gerçek dünyada yapılmaktadır. Gerçek dünyada yapılan ölçümler asla mükemmel olamaz. Ölçü aletlerinin, ölçmelerde her zaman duyarsız oldukları ve doğru ölçmedikleri sınırlar gibi sınırlamaları vardır.

Bütün deneysel ölçümlerin özünde var olan mükemmelsizliğe belirsizlik adı verilir. Yapılan her ölçümde her zaman belirsizliklerin var olduğu göz önünde bulundurulmalıdır.

Ölçme, bir büyüklüğü standart olarak kabul edilen bir büyüklükle karşılaştırma eylemidir. Bu eylemin sonucu, a) büyüklüğün standardın kaç katı olduğunu gösteren ölçü sayısı, b) birim ve c) ölçmedeki belirsizliği içeren hata terimleri şekilde yazılır. Ölçüm sonucunda ölçü sayısı ve birim bulunmazsa, eksik ifade edilmiş olmaz, hiçbir şey ifade edilmemiş olur. Hata terimi, tek veya çok sayıda yapılan ölçümlerde, ölçümün duyarlığını yansıtmaktadır.

Ölçü sayısı kullanılan ölçü aletinin duyarlılığını doğru göstermelidir. Bir ölçüm sayısında bulunması gereken sayılara anlamlı sayılar adı verilmektedir.

Bir ölçümün duyarlılık ve doğruluk olmak üzere iki niteliği vardır. Doğruluk, ölçülen değerin gerçeğe yakınlığını; duyarlılık ise tekrar eden ölçümlerin birbirlerine yakınlığını ifade etmektedir. Doğru olan bir ölçüm duyarsız olabilir, duyarlı olan bir ölçüm de doğru olmayabilir.

Duyarlılık, ölçenin ustalığı, aletin ve yöntemin duyarlılığı ve kalitesini içine alan ölçme işleminin kalitesini; doğruluk ise sonucun gerçeğe (standarda) olan yakınlığını yansıtır. Doğruluk sonucun kalitesi ile duyarlık ise bu sonucu elde etmek için kullanılan işlemin kalitesi ile ilgilidir.

Ölçmenin duyarlılığı standart sapma veya standart hata şeklinde yazılır. Standart sapma bir ölçümün duyarlılığının, standart hata ise ortalama değerin gerçek değere yakınlığının bir ölçüsüdür.

Deneysel sonuçlar amaca göre standart sapma veya hatadan biri kullanılarak, birim ile birlikte anlamlı sayılarla ifade edilir.

ABSTRACT

In an ideal world, measurements are always perfect. All measurements will have exact values and hence, calculations involving measurements will be simple. But, experiments are done in a real world, not an ideal world. In the real world case measurements are never perfect. Measuring devices have limitations such that there will always be imprecision and inaccuracies in measurements.

The imperfection inherent in all experimental measurements is termed an uncertainty. In the laboratory, uncertainties must always be considered every time a measurement is taken. Measurement is a comparison with a standard. In the end of measuring operation, result is reported as: a) figures that are equal the times of standard, b) unit, and c) error, uncertainty associated with measurement. If there are not figures and unit in the reporting result, we just say not incomplete, we say nothing. Error reflects the precision of a single measurement or repeated measurements.

Figures must represent true resolution of an instrument. Significant figures are all the digits in a physical quantity that have meaning or agree with the accuracy of the measurement of those physical quantities.

There are two features of a measurement: accuracy and precision. Accuracy reflects how close the result is to the true value. Precision is the ability to get the same results repeatedly. An accurate measurement may be imprecise and a precise measurement may be inaccurate.

Precision is the degree of refinement in the performance of an operation, or the degree of perfection in the instruments and methods used to obtain a result. Accuracy is the degree of conformity with a standard (the "truth"). Accuracy relates to the quality of a result, and is distinguished from precision, which relates to the quality of the operation by which the result is obtained.

In a repeated measurement, precision expressed as standard deviation or standard error of mean. Standard deviation is the degree of precision of a measurement and standard error of mean is the degree of closeness of the mean value to the true value.

Usually experimental results have to expressed together significant figures, unit and error terms.

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Nogo-A'nın Beyin Felci Sonrasında Hücre Yaşamına Olan Etkileri

Role of Nogo-A in Neuronal Survival in the Reperfused Ischemic Brain

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ÖZET

Aksonal rejenerasyonu engelleyen proteinlerden Nogo-A inhibisyonunun omurilik ve beyin hasarı sonrasında beyin plastisitesi ve fonksiyonel iyileşmeyi artırdığı bilinmektedir. Bununla beraber bu proteinin inhibisyonunun beyin hasarı sonrasında akut reperfüzyon hasarına olan etkileri ve mekanizmaları bilinmemektedir. Nogo-A knockout fare ve bu proteinin farmakolojik (anti-Nogo-A antibody:11C7) olarak inhibisyonu metotları kullanılarak yapılan çalışmalarda, beyin hasarı sonrasında ölüm oranlarında ve buna paralel olarak da apopitotik hücre ölümünde anlamlı bir artış gözlenmektedir. Yapılan protein analiz çalışmalarında, Nogo-A proteininin fonksiyonel olduğu farelerde RhoA'nın aktif, Rac1 ve RhoB'nin ise inhibe olduğu gözlenmektedir. Bunlara paralel olarak da stres kinazlardan p38/MAPK, SAPK/JNK1/2 ve bunlara ilaveten PTEN'nin aktivitelerinde düşme gözlenmektedir. Nogo-A proteininin inaktivasyonu sonrasında ise RhoA'nın inhibe, Rac1 ve RhoB'nin aktive olduğu, bunun sonucu olarak da p38/MAPK ve SAPK/JNK1/2 aktivitelerinde de artış gözlenmektedir. Aktivitesini kaybeden RhoA; Rock2 üzerinden PTEN'nin (Phosphatase-and-Tensin Homolog) uyararak Akt ve ERK1/2 yolaklarının inhibisyonunu takiben p53 üzerinden hücre ölümüne neden olmaktadır. Yapılmış olan bu çalışmalar Nogo-A'nın Rac1/RhoA dengesini kontrol ederek sinir hücresinin stres koşullarında hayatta kalmasındaki kritik rolünü göstermektedir. Ayrıca aksonal rejenerasyonu uyaran moleküller ile yapılacak olan klinik çalışmalarda bu etkilerin göz önünde bulundurulmasının önemini vurgulamaktadır. Bu sunumda yukarıda bahsedilen ve henüz yayınlanmamış çalışmalar tartışılacaktır.

Anahtar Kelimeler: Nogo-A, beyin felci, beyin plastisitesi, hücre içi sinyal iletimi ve apopitozis.

ABSTRACT

Nogo-A glycoprotein is an oligodendroglial neurite outgrowth inhibitor, the deactivation of which enhances brain plasticity and functional recovery in animal models of spinal cord trauma and ischemic stroke. Nogo-A's role in the reperfused brain tissue was still unknown. To elucidate this issue, we examined the effect of Nogo-A deactivation after transient focal cerebral ischemia. In mice, in which Nogo-A was constitutively deleted or inhibited with a neutralizing antibody (11C7) that was infused into the

lateral ventricle 24 hours prior to stroke, we show that Nogo-A deactivation goes along with decreased neuronal survival. Using protein expression and interaction studies we demonstrate that in the presence of Nogo-A the small GTPase RhoA is active, whereas Rac1 and RhoB are inhibited. As a consequence of Rac1 inactivation, stress kinase p38/MAPK, SAPK/JNK1/2 and phosphatase-and-tensin homolog (PTEN) activities low. Deactivation of Nogo-A, on the other hand, inhibits RhoA, at the same time overactivating Rac1 and RhoB, the former of which activates p38/MAPK and SAPK/JNK1/2 via direct interaction. RhoA deactivation in turn stimulates PTEN via its downstream effector Rho-associated coiled-coil protein kinase2 (Rock2), thus inhibiting Akt and ERK1/2, and initiating p53-dependent cell death. Our data suggest a novel role of Nogo-A in promoting neuronal survival by controlling Rac1/RhoA balance. Clinical trials should be aware of potential injurious effects of axonal growthpromoting therapies. Thus, Nogo-A antibodies should not be used in the very acute stroke phase. The above mentioned and unpublished studies will be presented.

Key Words: Nogo-A, stroke, brain plasticity, signal transduction and apoptosis.

Dynamics of Brain Rhythmogenesis in Human Sleep and Their Possible Contribution to Epilepsy

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ABSTRACT

Area specific and relatively higher frequency EEG oscillations are increasingly shown to be nested in and modulated by more widely synchronized slow rhythms. The respective phase and power relationships determine the rhythms' impact on several important brain functions and possibly the still mysterious impact of sleep on epilepsy (1). Brain activity during Non-Rapid-Eye-Movement (NREM) sleep is characterized by widely synchronous large slow waves, like K-complexes (KC) and delta waves. We observed two new phenomena suggesting that these slow waves may contribute to the generation of rhythmical activity of higher frequencies: (a) EEG time frequency analysis centred around the negative peak of the KC revealed that KC usually (in 812/1130) trigger spindles, which have significantly higher frequency (mean= 14.99 Hz) than that of spontaneously occurring fast centroparietal spindles (14.13 Hz; p< 0.00002) and of course slow frontal spindles (12.02 Hz). When KC occur during spontaneously running fast spindles (n= 400) they invariably interrupt them and replace them by a short slower rhythm (~ theta) before they trigger (135/400) a new spindleo rhythm of invariably higher frequency (by m= 1.17 Hz). (b) Magnetic Field Tomography analysis of MEG records during NREM sleep "core" (i.e. CAP-B) periods revealed very high gamma frequency activations localized in the left dorsomedial prefrontal cortex, developing in parallel to the NREM stages to culminate in NREM-4 and expanding laterally in REM. Both spindles and gamma frequency rhythm are considered to be paced by thalamocortical circuits. The time (a and b) and space (b) characteristics of the two described phenomena suggest that both may develop from a mechanism of cortical disinhibition affecting thalamocorical pacing circuits and expressed as a rebound in time after the inhibitory negative phase of the KC (in a) or as lateral disinhibition in space promoting the generation of gamma activity in the centre of areas with highest delta activity (in b). The above findings are respectively considered in the context of efforts to explain two types of epilepsy: absence seizures in relationship to thalamocortical circuits generating sleep spindles and frontal lobe nocturnal seizures in relation to gamma frequency activation of midfrontal regions during NREM sleep.

Key Words: Sleep, rhythms, epilepsy.

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Sirkadiyen Ritimler ve Leptin Hormonu

Circadian Rhythms and Leptin Hormone

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ÖZET

Mevsimsel hayvanlar yağ dokularında, besin alımında ve enerji metabolizmalarında yıllık sikluslar gösterir. Bu sikluslar melatonin hormonunun diürnal profilinin oluşmasına ve nöroendokrin yollar üzerinde etkili olmasına neden olan dışsal gün uzunluğu sinyallerindeki değişimler tarafından tetiklenir. Hayvanlar mevsime özel birçok değişik davranış ve fizyolojik adaptasyonlar gösterir. İki tip endojen (içsel) zaman koruyucu mekanizma hayvanların mevsimlere göre adaptasyonunu sağlar; bunlardan biri zamanlayıcı olarak adlandırılan yapıdır ki bu ayların aralıklarını ölçer, diğeri de saat olarak adlandırılır ki bu da yıllık periyodu hesaplar. Burada zaman koruyucu mekanizmalara ait temel prensipleri ve moleküler yapıları tartışmaya çalışacağım; ayrıca bunların güvenilirliğini ve çevresel faktörlerin mevsimlerle olan iş birliğini anlatacağım. İlk başlarda bu 2 saat mekanizmasını birbirinden ayırıp yapılarını açıklamak faydalı olduysa da, karşılaştırmalı hayvan fizyolojisindeki bulgular özellikle leptin salınımında, ortak noktaları işaret etmeye başladı. Beyaz yağ doku hormonu olan leptin mevsimsel hayvanlarda vücut ağırlığı mekanizmalarını düzenler ve dolayısıyla salınımında mevsimsel değişimler gözlenmektedir. Mevsimsel üreyen Suriye hamsterleri laboratuvarlarda çok kullanılan bir hayvan modelidir, çünkü; sirkadiyen ritimleri düzenleyen saatin (SCN) enerji metabolizması üzerine, iştahın düzenlenmesine ve şişmanlığın kontrol mekanizmalarını aydınlatma konusunda yapılan çalışmalara kısa zamanda yanıt vermektedir. Yaptığımız bir çalışmada değişik dozlarda verilen leptin hormonu Suriye hamsterlerinde faz kaymalarına neden olmuştur. En büyük kaymanın ise direkt SCN bölgesine yapılan uygulama ile olduğu görülmüştür. SCN ve leptin arasındaki ilişkiler yeni yeni aydınlatılmaya başlanmış olup, sonuçlar obezite açısında umut vericidir.

Anahtar Kelimeler: Fotoperiyod, melatonin, leptin, SCN.

ABSTRACT

Seasonal animals exhibit annual cycles of adiposity, food intake and energy metabolism. These cycles are driven by changes in the external daylenght signal, which generates a diurnal melatonin profile and acts on neuroendocrine pathways. Animals have evolved many season-specific behavioural and physiological adaptations that allow

them to both cope with and exploit the cyclic annual environment. Two classes of endogenous annual timekeeping mechanisms enable animals to track, anticipate and prepare for the seasons: A timer that measures an interval of several months and a clock that oscillates with a period of approximately a year. Here, I discuss the basic properties and biological substrates of these timekeeping mechanisms, as well as their reliance on, and encoding of environmental cues to accurately time seasonal events. While the separate classification of interval timers and circannual clocks has elucidated important differences in their underlying properties, comparative physiological investigations, especially those regarding seasonal leptin secretions, hint at the possibility of common substrates. The white adipose tissue hormone leptin reflects overall adiposity in seasonal mammals, and consequently undergoes significant seasonal fluctuations in secretion. The seasonally breeding Syrian hamster is a convenient laboratory model to study the effects of a seasonal time-keeping clock on energy metabolism, appetite regulation and the control of adiposity. We have shown that administration of exogenous leptin in different doses induces significant phase advance in hamsters kept in constant darkness. The biggest phase advance was observed in intra-SCN infusion and the smallest was in ip injection hamsters.

Key Words: Photoperiodism, melatonin, leptin, SCN.

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Dazed and Confused: Corticospinal Reorganization Associated with Disuse Atrophy

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ABSTRACT

Prolonged reductions in muscle activity and mechanical loading (e.g., bed rest, cast immobilization) result in dramatic reductions in muscle strength and function. We have previously reported that 3-weeks of immobilization results in a decreased ability of the nervous system to maximally activate muscle (1), and that these deficits account for ~50% of the between-person variability in the loss of strength following 4-weeks of lower limb unweighting (2,3). Our most recent work has evaluated the time course of these neural adaptations, and determined specific adaptations in corticospinal properties. This presentation will detail our findings regarding human neuroplasticity associated with disuse. This work utilizes a combination of techniques involving nerve stimulation and transcranial magnetic stimulation to assess changes in central activation of muscle, along with spinal (H reflex) and corticospinal excitability (i.e., motor-evoked potential amplitude, silent period) and contractile properties of healthy humans undergoing 3-4 weeks of forearm cast immobilization and/or lower limb unweighting. Collectively, this work has indicated that immobilization results in deficits in neural activation of muscle, and illustrate the profound physiological and functional effect of immobilization on the human nervous system as evidenced by the alterations in corticospinal excitability persisting for over 1 week following cast removal.

Key Words: Immobilization, bed rest, strength.

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Group Creativity and Interdisciplinary Teamwork

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ABSTRACT

It is often assumed that group interaction or teamwork enhances creativity or innovation, especially in cases where the group or team members have diverse expertise, perspectives, or backgrounds. Much research has found that this assumption is often not warranted. Our research in the past 20 years has examined the factors that enhance and inhibit creativity in groups. This has led to the development of a social-cognitive model of group creativity. For groups to excel in the creative process, group members need to have both the capability and motivation to process the shared ideas and information and to combine these in unique ways to develop useful innovations. Most of our research has focused on the idea sharing aspect of group creativity. I will summarize our major findings and their theoretical implications. In particular, I will discuss the relevance of our work for interdisciplinary teamwork. I will also highlight recent efforts by our team to understand the neural underpinnings of the group creative process.

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Seizures in Developing Brain and CNS Cholinergic Neurotransmission

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ABSTRACT

Immature brain activity influences the course of its development. For example, extreme patterns of activation or lack of activation may cause aberrations from normal brain maturation that can be experimentally or clinically detected in adult brain. Epilepsy, a brain disorder caused by the propagation of brain waves of highly synchronized excitatory potentials is manifested in infancy or childhood; moreover, certain epileptic syndromes are associated with cognitive deficits in adulthood. Experimental epilepsy models provide the means to study the impact of overly synchronized CNS neuronal activity in brain development, by comparing a variety of functional or anatomical indices in naive versus "epileptic" age-matched animals.

Brain cholinergic receptors are involved in cognitive processes, and changes in their numbers or properties have been detected in dementias. The work of my group focuses on the long term effects of early life seizures. These are provoked by the administration of pentylenetetrazol (PTZ), a $GABA_A$ receptor antagonist at postnatal day 20 rat pups, while experiments take place in adult animals. Our findings include the following, (a) we have established that changes in cholinergic (muscarinic) receptors occur, by recording electophysiological potentials in vitro in rat brain slices; (b) we have investigated the cellular mechanisms of the observed effects; (c) we have tested for differences in the behavior of adult PTZ-conditioned rats by using specific tests such as open field activity, object recognition and "depressive-like behavior". In two of the three axes of our research (b,c), where we also differentiated between male and female conditioned animals, we detected gender associated differences.

We expect that our findings will contribute towards understanding the effects of early life seizures on the basic (cellular) level of adult brain function and also towards linking such changes to behavior. By doing so, we also hope to unravel some of the mechanisms that underlie the activity-dependent immature brain plasticity.

Key Words: Hippocampus, immature brain, muscarinic receptors, electrophysiology.

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Beyin Yaşlanması

Brain Aging

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ÖZET

Beyin yaşlanması, nöral plastisitedeki değişiklikler veya bu değişiklikleri etkileyen mekanizmalardaki farklılaşmalardan dolayı duyularda, idrak kabiliyetinde, bellek ve motor kontrolde azalmayla birlikte görülür. Normal yaşlanma sürecinde gerçekleşen fonksiyonel değişiklikler ve bu değişikliklerin selektif bilişsel bozukluklara ve ileri yaşlarda oluşan nöronal plastisiteye nasıl katkıda bulunduğu biyolojinin yoğun çalışılması gereken alanlarından biridir. Postmortem insan beynindeki çalışmalar gösteriyor ki beyin ağırlığında %0.1/yıl gibi küçük bir azalma olmaktadır. Bu azalma 50 yaşından sonra çok daha hızlıdır ve beyin ağırlığındaki bu hızlı azalma beynin beyaz cevherinde difüz ve düzenli fakat gri cevherde bölgesel değişiklikler göstermektedir. Örneğin; frontal ve pariyetal korteks temporal ve oksipital korteksten daha fazla etkilenir. Ağırlıkta olduğu gibi beyin hacim azalması da yaşla (yaklaşık %0.1-0.5/yıl) artmaktadır. İlk başlardaki çalışmalarda, araştırmacılar yaşla esaslı bir nöron kaybının oluştuğunu rapor etmişlerdir. Ancak son zamanlardaki çalışmalarla yaşla nöron kaybının çok az olduğu sonucuna varılmıştır. Özellikle beyin korteksinde, yaşla nöron boyutu da azalmaktadır. Dendritik spine sayısında yaklaşık %50 düşüş ve dendritik dallanmada anlamlı ölçülerde büzüşme saptanmıştır. Ayrıca, astrosit ve mikrogliaların sayı ve boyutu yaşla artmaktadır. Bunlar aktive olduklarında bazı durumlarda nöroprotektif olduğu gibi patojenik de olabilir.

Beyin yaşlanmasındaki diğer önemli bir neden de bir organizmanın yaşam süresi boyunca nöronların yüksek enerjiye olan ihtiyaçlarıdır. Nöronların enerjiye olan yüksek ihtiyacı onları yaşlanmaya karşı kolayca duyarlı hale getirir. Nöronların büyük boyutları nedeniyle; çok geniş membran yüzeyleri; molekül ve organallerin hücrenin uzak yerlerine transportu ve impuls iletiminde kullanılan elektrik aktivitesi için gerekli iyon gradiyenti onları yüksek miktarda enerjiye bağımlı yapar. Mitokondride enerji üretiminde görevli elektron transport sisteminde meydana gelen süperoksit iyonunun sızması sonucunda hidroksil radikalleri, peroksinitrit ve hidrojen peroksit gibi yüksek reaktif oksijen türevleri meydana gelmektedir. Bu moleküller proteinleri, yağları ve nükleik asitleri okside ederek beyinde oksidatif hasara sebep olur. Oksidatif stresin belirgin etkisi mitokondride görülebilir, çünkü serbest radikallerin çoğu bu organellerde üretilir. Koruyucu histonların eksikliğinden dolayı özellikle mitokondriyal DNA hasar görebilir. Bu yüzden yaşlanan beyinde, mitokondriyal fonksiyon bozukluğu ve kompleks I, II ve mtNOS gibi beyin mitokondriyal enzim

aktivitelerinde azalma görülmektedir. Bu enzimlerin aktiviteleri; nörolojik performans ve yaşam süresi ile pozitif, mitokondriyal yağ ve protein oksidasyon ürünleri ile negatif korelasyona sahiptir. Yaşlanan beyinde mitokondri kalsiyum gradiyenti değişmiştir ve mitokondri depolarizedir. İmpuls iletimi sürecinde bu iyonun konsantrasyonu yükseldiğinden mitokondriyal membranlar sitozolden kalsiyum iyonunu alır. Yaşlanan mitokondri özellikle eksitasyondan sonra olmak üzere kalsiyumu depolayamaz ve bu yüzden sitozoldeki kalsiyum konsantrasyonu yükselir. Eksitasyon, sağlıklı genç nöronlarda da voltaj bağımlı kalsiyum ve NMDA glutamat reseptör kanallarını açar ve hücre içi kalsiyum seviyelerinde geçici yükselmeye sebep olur. Bu normal yaşlanmada artmıştır. Hücre içi kalsiyum seviyelerindeki yükselme hücrelere zarar veren kalsiyum bağımlı kaspazları aktif hale getirebilir. Hatta apopitozla hücre ölümüne sebep olabilir. Ancak muhtemelen apopitozun dendritlerle sınırlı kalmasına sebep olur. Yaşlanan beyinde, bozulmuş kalsiyum homeostazı, impuls transmisyonunu ve nörotransmitter salınımını bozamaz, fakat beyni hafif hipoksi gibi stres durumunda kolayca hasarlara açık hale getirir. Yaşlıların çoğu genellikle geçici hipoksik epizodlara sebep olabilen serebrovasküler ve kalp rahatsızlığına sahiptir. Hipoksi, postsinaptik membranlarda NMDA reseptörlerini açan ve sitozolik kalsiyumu yükselten glutamat salınımına sebep olabilir. Apopitoz yaşlanmayla birlikte nöron kaybının sebebi olan nöron ölümünün tek yolu değildir. Ayrıca, özellikle dendritik spine kaybında muhtemelen apopitoz dışındaki diğer nöron ölüm yolları etkili olmaktadır.

Demir ve lipofussin yaşla birlikte beyinde birikir. Yüksek miktarda demir ayrıca oksidatif stresi de artırır. Lipofussin proteinlerin lizozomal parçalanmasından üretilen maddelerden oluşur. Lipofussin birikimi otofaji sisteminin bozukluğuyla ilgilidir. Bu yüzden otofaji beyin yaşlanmasında çok önemlidir.

Yaşlanmayla ilgili diğer bir değişiklik de "advanced glycated end products AGEs"lerin oluşumudur. AGEs nükleik asitler, proteinler, lipidlerin amino grupları ile indirgenmiş şekerler arasında nonenzimatik olarak meydana gelen çapraz bağlanmalarla üretilir. AGEs beyni de içeren farklı dokularda kolayca büyük kütlelere agrege olabilir ve proteozomal protein yıkımın mekanizmasından kaçabilir, sonuçta oksidatif stres oluşumuna neden olur.

Sinaptik fonksiyon ve plastisite, veziküler transport, kalsiyum homeostazı, nörotropin sinyal iletimi, nöronal ubiquitin-proteozom sistemi, mitokondriyal dinamik ve fonksiyonunu içeren pek çok genin ekspresyonu 40 yaşından sonra azalır. Diğer taraftan; protein katlanması, stres cevabı, antioksidan savunma, metal iyon homeostazı ve inflamatuvar yanıtı içeren genlerin ekspresyonunda artış bazı son çalışmalarda gösterilmiştir.

Nörodejeneratif hastalıklarda, mutant ve yanlış katlanmış proteinler, bunların ubiquitin proteozom sistemi tarafından yetersiz yıkılımı sebebiyle hücrelerde birikir. Nörodejenerasyonun moleküler patogenezinde bu sistemin aktivitesinin kritik bir rolü vardır. Ubiquitin proteozom sisteminin sinapsların devam ettirilmesinde de rolü vardır. Bu sistem göreceli olarak yaşlanan hücrelerde hasar görmüştür. Bu yüzden proteinler agrege olur ve bu agregatlar ubiquitin proteozom sistemine hasar verir, akson transportunu ve sinaps fonksiyonunu bozar.

Kalori kısıtlamasının, mayadan insana kadar çeşitli organizmalarda maksimum yaşam süresini sağladığı biliniyor. Son çalışmalar ayrıca göstermiştir ki kalori kısıtlaması beyin yaşlanmasını geciktiriyor ve yaşla oluşan nörodejeneratif hastalıkların oluşmasını erteliyor. Kalori kısıtlamasının yararlı etkilerini taklit edecek tedavi girişimlerinin geliştirilebilmesi için, kalori kısıtlanmasının nöroprotektif etkilerinde rol oynayan mekanizmaların aydınlatılması gerekmektedir. Kalorik kısıtlaması BDNF gibi nörotropinler, transkripsiyon faktörleri (FOXO, PPAR), sirtuinler ve nörogenezi artırır. Obezite, fazla kalori alımı, yüksek serum lipid, kolesterol, homosistein düzeyleri ve yüksek kan basıncı metabolik sendroma sebep olur ve serebrovasküler hastalıklar ve Alzheimer için risk faktörleridir.

Egzersiz, poliansature yağ asidi kullanımı, B_{12} vitamini, folat beyin fonksiyonlarını olumlu etkileyen diğer faktörlerdir.

ABSTRACT

Brain aging is associated with decline in sensation, cognition, memory and motor control due to the changes in neural plasticity or alterations that affect mechanisms of plasticity. Functional alterations that occur during normal aging and how these age assosiated changes might contribute to the selective cognitive impairments and neuronal plasticity that occur in advanced age is the area of biology that should be intensively studied. Studies of post mortem human brains indicate that there is a small loss of brain weight of about 0.1%/year. This lost ıs much more rapid after age 50 and more rapid brain weight decrease is diffuse and uniform in cerebral white matter but shows some regional differences in grey matter. For example frontal and parietal cortex more affected than temporal and occipital cortex. Same as weight, brain volume reductions is also increases with age (about 0.1-0.5%/year). In initial studies, The researches reported that substantial neuron loss occurs with age. However recent Works concluded that neuron loss with ageing is very low. Neuron size is also decrease with age, especially in cerebral cortex. Aproximently 50% of reduction in spine number and significantly shrinkage of dendritic trees have been determined. The number and size of astrocyes and microglias are also

increase with aging. They can be pathogenic when activated as well as neuroprotective in some conditions.

Another important cause in brain aging is high need of energy of neurones during the life span of an organism. The high energy need of neurones make them vulnerable to aging. Because the big size of neurones, their very large membrane surface, transportation of molecules and organels to distant parts of the cell and ion gradient nesesary for the electric actity required for impulse transmission makes them dependent on high amount of energy. The leakage of superoxide ion radical occured in electron transport system during the production of energy in mitochondria and lead to generation of highly reactive oxygen species, such as hydroxyl radicals peroxynitrite, hydrogen peroxide. These molecules oxidize proteins, lipids and nucleic acids causing oxidative damage in the brain. The profound effect of oxidant stress can be seen in mitochondria because most of the free radicals is produced in these organeles. Especially mitochondrial DNA can be easily dameged because of the lack of protective histons. Therfore aging brain ıs associated with the impairment of mitocondrial function and decreased activities of brain mitochondrial enzymes such as complexes I, II and mtNOS. The activities of these enzymes have pozitive correlation with neurological performance,life span and negative correlation with mitochondrial lipid and protein oxidation products. In aging brain mitochondria calcium gradient across mitochondrial membranes altered and mitochondria are depolarized. Mitochondrial membranes take up calcium ion from the cytosol when concentration of this ion increased during impulse transmision. Aging mitochondria failed to store calcium and therefore the concetration of calcium in the cytosol is increased, particularly after excitation. Excitation opens voltage-dependent calcium and N-methyl-D-aspartate (NMDA) glutamate receptor channels and leads to a transient rise in intracellular calcium levels, even in healthy young neurons. This is increased in normal ageing. Elevated levels of intracellular calcium can activate calcium-activated caspases, damage the cells. Even cause cell death by apoptosis. However it possibly cause apoptosis limited to dendrites.In the ageing brain, disrupted calcium homeostasis can not disturbe impulse transmission and neurotransmitter release, but renders the brain very vulnerable to damage if there is a stressful condition like mild hypoxia. Most of elderlies usually have cerebrovascular and heart diseasewhich can cause transient hypoxic episodes. Hypoxia can lead to relase of glutamate which open NMDA receptors on post synaptic membranes and increase cytosolic calcium. Apoptosis isn't the only mode of neurone death responsible for the loss of neurone with aging. Other mode of neurone deaths is also effective especially in dendritic spine loss.

Iron and lipofuscin are accumulated in the brain with age. Increased amount of iron can also give rise to oxidative stres. Lipofuscin is consist of substanses that produced from lysosomal degradation of proteins. Lipofussin accumulation is related to failure of autophagal system. Therfore autophagy is very impotant in brain aging.

Another change with with aging is production of advanced glycation end-products (AGEs). AGEs are product of cross-links non-enzymaticaly generated between amino groups of nucleic acids, proteins, lipids and reducing sugars. AGEs can be easily agregate into big messes in different tissues including brain and escape from proteosomal protein degrading machinery leading to generation of oxidant stres.

Expression of many genes involved in synaptic function and plasticity, vesicular transport, calcium homeostasis, neurotrophin signaling, neuronal ubiquitin-proteasome system, mitochondrial dynamic and function were reduced after 40 years old. On the other hand , expression of the genes involved in protein folding, stres response, antioxidant defence, metal ion homeostasis and inflamatory responce was shown to be increased İn some recent gen expression studies.

In neurodegenerative diseases, mutant and misfolded proteins accumulate in the cells because of insufficient degredation of them by ubiquitin proteosome system. The activity of this system has a crutial role in the molecular mechanism involved in pathology of neurodegeneration. Ubiquitin proteosome system has also a role in the maintenance of synapses. This system is relatively disrupted in aging cell. Therefore proteins agregate and this agregates further distrupt this system and affect the axonal transport and the function of synapses.

Caloric restriction is known to extend maximum liespan in several organisms from yeast to human. Recent studies also showed that caloric restriction delay brain aging and retard neurodegenerative diseases with aging. Molecular mechanisms involved in neuroprotectiv effect of caloric restriction should be investigated due to therapeutic interventions aimed at mimicing the beneficial effect of caloric restriction. Caloric restriction increase neurotrophines, such as BDNF, transcription factors (FOXO, PPAR), sirtuins and neurogenesis. Obesity, excess calorie intake, increased serum lipid, cholesterol, homosistein levels and high blood pressure lead to metabolic syndrome and are risk factors for the cerebrovascular and Alzheimer's diseases.

Exercise, usage of polyunsaturated fatty acids, vitamin B_{12}, folate are other factors that positively effects brain functions.

Postür ve Yürümenin Fizyolojisi

Physiology of Posture and Gait

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ÖZET

Hareket etmek (lokomosyon) hayvanlarda canlılığın en önemli davranışlarından biridir ve paleozoik evreden bu yana evrimleşen canlılarda gözlenmektedir. Yürümek, beden kütlesinin basitçe bir yer değiştirmesi değildir; bilinçli bir davranış ile "bir yerden bir yere gitmek"tir. Böylesi bir "amaç"lı davranış için serebral korteksten kol ve bacak/ayak kaslarına kadar bir dizi organ ve sistem iyi organize edilmiş ve uyumlu işlev gösterir.

Yürümenin en alt birimi miyotatik refleks arkı olup gerilme reseptörü olarak grup Ia lifleri ile sağlanır. Yürüme esnasında aynı ekstremitede iki miyotatik ünit antagonistik olarak çalışır. Kontralateral identik kaslarda da agonist-antagonistik mekanizma işlev görür. Böylece bir bacak adımlamanın salınım fazını yaşarken diğer bacak basma fazını sürdürebilmektedir. Segmental aferent ve eferentlerden oluşan miyotatik refleks arkı, yine omurilik düzeyinde bir sentral patern jeneratöre sahiptir. Bu işlev yürüme hareketlerinin ardışık sürdürülmesini sağlar ve insanda da gösterilmiştir. Tek bacağın bu şekilde ritmik hareketleri "yarım merkez" kavramıyla açıklanmıştır. Bu şekilde, bir bacağın fleksörü ile diğer bacağın ayni segmentteki ekstensörü -senkronize bir şekilde- aktive olmaktadır (co-activation). Spinal patern jeneratör düzeltici işlevlere de sahiptir. Yürümede denge ve postüral adaptasyon ile ilgili serebellar ve vestibüler sistemlerden gelen inici etkiler de çok önemlidir.

Deneysel olarak ön bacak aferentlerinin arka bacak motor nöronlarıyla ve arka bacak aferentlerinin de ön bacak eferentleriyle doğrudan ve oligosinaptik bir bağlantı içinde olduğu gösterilmiştir. Bu kısa intraspinal bağlantı sistemi insanda da gösterilmiştir. Biped yürüme halindeki insanda da yürüme esnasında kol ve bacaklarda çapraz koaktivasyon (sol bacağın fleksiyonu esnasında sağ kolun fileksiyonunun sağlanması gibi) oluşmaktadır.

Miyotatik refleks arkı ve sentral (spinal) patern jeneratörün fizyolojik yürümeyi sağlamada yetersiz kaldığı bilinmektedir. Süperior kollikulusun altından kesi yapıldığında yürüme bandı üzerinde hayvanlar yürüyebilmekte hatta koşabilmektedirler (Hinsey ve ark. 1930). 3 mm daha aşağıdan kesi yapıldığında ise bu yetenek ortadan kalkmaktadır. Mamillotalamik bölgenin elektriksel uyarımları ile yürüme gösterilmiştir. Mezensefalonda yapılan uyarımlarla da yürüme oluşturulabilmiştir. Bu alandaki hücrelerin pedinkulopontin nükleus içindeki nöronlarla kolinerjik bağlantılar göstermiş olması önemlidir. Bu hücrelerin efernetleri

ise BSRF içinde özellikle nucleus retikülaris magnocellularis ve gigantocellularis'e ulaşmakta ve burada yoğun bir şekilde retikülospinal yollar ile ventral omurilikte ilgili segmentlere ulaşmaktadır. Bu sistem sadece ritm yaratıcı değildir; yürümede gereken kuvveti de yönlendirir. Nitekim, bu hücrelerdeki boşalımların yürüme fazları ile ilişkili olduğu gösterilmiştir. Serebellum eferentleri de bu sistem üzerinde etkindir. Piramidal hücreler spinal pattern generatörde siklusu etkilemekte ve ritmi modüle edebilmektedir. Ancak, piramidektomize hayvanlarda kısa bir süre sonra yürümenin yeniden kazanıldığı gösterilmiştir. Bu gözlem ise yürümenin kortikal düzeyde piramidal sistem dışındaki diğer motor hücreler tarafından da kontrol edildiğini göstermektedir. Piramidal hücrelerin becerili yürümede rolü olduğu bilinmektedir. Sensoryel korteksin de bu beceride rolü olduğu bilinmektedir. Bu şekilde korteksin bilinçli korrektif davranışları ve yürümenin modunu belirlediği anlaşılmaktadır.

Anahtar Kelimeler: Lokomosyon, postür, spinal pattern jeneratör, yürüme.

ABSTRACT

Locomotion is a complex behaviour and, seen in animals since paleozoic ages. Gait is, however, not a simple transfer of the body mass; conversely, it is a conscious and purposeful behaviour as "going to somewhere from another". A well-organized anatomo-physiological system(s) from cerebral cortex to the leg muscles is established for this purpose.

The lowest unit of stepping is myotatic reflex which is mediated by group-I fibers. Flexors and extensors in the same and contrlateral legs innervated reciprocally contract or relax during stepping; so, one of the legs moves in swing phase while the contrlateral one stances. The cyclic phase of stepping is organized by central pattern generator (CPG) within the lumbosacral spinal cord. The presence of CPG in humans has been demonstrated by clinical and electrophysiological studies. The cyclic pattern of leg movements in one extremity is explained by "half center" hypothesis. CPG, furthermore, has corrective control of stepping. Descending cerebellar and vestibular influences on the organisation of posture and gait have also great importance.

Direct, oligosynaptic circuits between the afferents and efferents of fore-and hindlimbs of animals have been demonstrated. This short interlimb assembly has been shown in humans as well. Crossed co-activation of leg and arm muscles in humans, walking bipedally in erect posture, is coordinated by this anatomo-functional organisation.

It is obvious that neither CPG nor myotatic reflex unit can simply and uniqely make possible normal gait although experimental animals could walk and run on the treadmill even when transected at the level caudal to superior colliculus. If a second transection at the level 3 mm more caudal was made the animals can not walk any more. Electrical stimulation of this mamillothalamic area, called as subthalamic locomotor area, produce walking movements in animals. Similarly, electrical stimulation of some mesencephalic neurons (mesencephalic locomotor region) that have synaptic relations to those located in pedinculopontin nucleus of which efferents involve the descending influences of reticulospinal tract via the nucleus reticularis magnocellularis and gigantocellularis provides stepping in experimental animals. This system affects motor performance, rather than cycling of stepping movements. Cerebellar efferents have also been considered in this performance. On the other hand, pyramidal cortical cells take over the control on CPG and regulates the rhythm and cycle of the stepping although reorganisation of stepping and gait has been observed after removal of pyramidal cortex (pyramidectomized animals). These observations suggest that cortical control of gait is provided not only by the pyramidal system but also by some other neuronal systems such as those located at the primary sensory cortex and prefrontal cortex.

Key Words: Locomotion, posture, central (spinal) pattern generator, gait.

Yapay ve Biyolojik Nöron Ağlarında Bilginin Temsili

Knowledge Representation in Artificial and Biological Neural Networks

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ÖZET

Psikolojinin en önemli araştırma konusu zihinsel faaliyetin nasıl meydana geldiğini ve bilginin beyinde nasıl temsil edildiğini anlamaktır. Bu konu yüzyıllarca bilim insanlarının ilgisini çekmiş ve buna bir cevap bulmaya çalışmışlardır. Zihinsel faaliyetin, beynin çalışmasının ürünü olduğu bilinmekle birlikte, beynin bunu nasıl olup da gerçekleştirdiği yakın zamana kadar bir bilmece olarak kalmıştır.

Yapay nöron ağları, birbirlerine çok sayıda sinaps ile bağlı ve bu sinapslar aracılığıyla birbirlerine uyarıcı ya da bastırıcı sinyaller gönderen bir grup nöronun bilgiyi nasıl işlediğini (nasıl kompütasyon yaptığını) araştıran bir çalışma alanıdır. Bu konunun temelleri, 50 yıl kadar önce, bilişsel fonksiyonların nöronal aktiviteye nasıl dayandırılabileceği üzerine kafa yoran 2 araştırmacı olan McCullogh ve Pitts tarafından atılmıştır. Bu çalışmacılar, özel bir yapıya sahip ve basit yapay nöronlardan oluşan bir ağın, bütün mantıksal ifadeleri temsil edebileceğini, yani -kuramsal olarak- genel amaçlı bir bilgisayar gibi davranabileceğini göstermişlerdir. Yapay nöron ağları, biyolojik ağların bilgisayarda yaratılan basitleştirilmiş modelleri olup,

1. Bilgiyi depolayabilirler ve çağrışımsal bellek gibi görev görebilirler.

2. Yeni şeyler öğrenebilme yeteneğine sahiptirler ve bunun için eğitilebilirler.

3. Yapay nöron ağları hataya son derece dayanıklıdırlar. Nöron ya da sinapslarının küçük bir kısmı yok edilse bile, bir miktar performans kaybı ile çalışmaya devam edebilirler.

Bu konferansta yapay nöron ağları giriş düzeyinde ele alınarak tanıtılacaktır. Değişik örneklerle, buağların bilgiyi nasıl kodladıkları ve kodlamadaki değişikliğin ağın işlevini nasıl değiştirdiği üzerinde durulacaktır.

Anahtar Kelimeler: Yapay nöron ağları, zihin-beden sorunu.

ABSTRACT

Psychology's most important research problem is the mind-body problem, that is to understand the way the mind is related to the body. Though it's known that mental activity is the result of the working of the brain, the

way the brain accomplish this task still remains a mystery. Artificial Neural Networks (ANN) is a relatively new branch of the cognitive sciences, which claims to have an answer to that mystery. ANN's are mathematical models of biological neurons which consist of a group of processing units with a large number of interconnections and send each other excitatory or inhibitory signals. The field is started in 1943 by McCullogh and Pitts, in an effort to understand how mental processes arise in the brain. They showed that any finite logical expression could be implemented by an appropriate net of simplified artificial neurons. That is they can act (in theory) as general purpose computers.

ANN's have interesting properties which resembles the human brain:

1. They can store knowledge and act as associative memories. Information is represented in the strength (the ability of a synapse to transmit its incoming signal) of their synapses.

2. ANN's are capable of learning and can be trained. They can generalize, learn characteristics of a category by seeing only a small number of specific examples.

3. ANN's are highly fault tolerant. They can continue working, only with a slight deterioration of performance, even after a small number of its neurons and/or synapses are removed. The loss in the performance parallels the number of the neurons removed. This property is highly reminiscent of the clinical picture seen in degenerative dementias like Alzheimer's disease.

Key Words: Artificial neural networks, mind-body problem.

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