***Field:* Neuroscience/Medicine**

Introductory Speakers:

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Session Topic:

Mechanisms of chronic pain

Title: Mechanisms of chronic Pain

Introduction

This session will focus on mechanisms of acute and chronic pain. According to the definition pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Hence, pain is primarily a vital sense warning against tissue damage. Unfortunately, in many patients pain has lost its physiological warning function but has become a disease of clinical significance, itself. Several somatic and psychological conditions may cause such a chronic manifestation of pain. Suffering from chronic pain is a common cause of individual impairment and harm all over the world often leading to distinct reduction in the quality of life. Furthermore, pain and especially chronic pain is an enormous problem for health care policies and presumably the most common and expensive disease leading to medical attendance in central Europe.

Given the multiple facet of pain, pain research is a multidisciplinary research field including physicians, molecular biologists, physiologists, geneticist, psychologists, etc. that work in cooperation on mechanisms of development, progression and maintenance of pain as well as of its specific therapy on molecular, somatic and psychic basis. Fortunately, enormous scientific progress was achieved within the last years regarding peripheral and central mechanisms that lead to acute or chronic pain. Several transducer molecules have been identified and characterized that are particularly activated by those tissue damaging stimuli in the periphery and that excite - alone or in concert with others - specifically the peripheral pain sensing neurons. Numerous processes were identified that are initiated by the different aspects of pain and that lead to a modified pain processing within the central nervous system. Functional testing *in vivo* increasingly identifies areas within the brain that are activated by the emotional experience pain. New methods were established that make the subjective pain perception measurable - which thus enable clinical studies and worldwide comparison of the results. This enormous growth in knowledge of molecular, cellular and systemic mechanisms underlying nociception and pain will have important implications for the clinical diagnosis and therapy of pain. A challenge for the near future will be to transfer those basic research results from the laboratories into the clinics for the welfare of pain suffering patients. Using those multidisclipinary approaches may soon lead to a mechanism-based classification of the different pain syndromes and hopefully enable a more rational treatment in the near future.

After an introduction into the principle mechanisms of peripheral and central processing of painful stimuli within the nervous system, methods in basic and clinical pain research will be presented as a start of the session. Using data obtained from different cell model systems *in vitro*, as well as in healthy volunteers and patients *in vivo*, the first talk will generally introduce into the topic of pain research. Prof. Dr. Martin Schmelz from the

Department of Anesthesiology of the university hospital of Mannheim, Germany, will afterwards demonstrate some translational aspects of basic pain research. In his talk he will present methods used to examine how painful stimuli may specifically activate peripheral pain sensing neurons and how that information is propagated into the central nervous system. He will also address the questions what we may deduce from the different experimental models used and in which way these results may change pain therapy in future. Prof. Dr. Takahiro Ushida, from the Multidisciplinary Pain Center of Aichi Medical University, Japan, will talk about mechanisms that induce chronic pain during immobilization or by other forms of disuse of a limb. In the animal model that he will demonstrate removal from peripheral sensory information and motor activity also induces continuous plastic changes within the central nervous system that may induce chronic pain as well. Understanding these mechanisms may ultimately lead to a better prevention of pain syndromes within the musculoskeletal system that are, unfortunately, at present very common and difficult to treat (e.g. chronic back pain).

General review: Pain and chronic pain

According to the International Association for the Study of Pain – IASP – pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Stimuli which cause pain are usually liable to destruct normal tissue or would potentially do so if acting prolonged. These stimuli - such as noxious heat, cold, mechanic pressure or numerous chemicals - permanently threaten integrity of our bodies. Thus, pain is primarily an extremely necessary, substantial and vital sense which warns us against tissue damage. For that purpose most tissues are densely innervated by special nerve fibres - the so-called nociceptors – which are specifically activated when those destructive stimuli hit the body. This specific activation of neurons of the sensory nervous system by actually or potentially tissue damaging stimuli is called nociception. Respecting the manifold stimulus modalities capable of damaging tissues and the fact that this warning system has to initiate when harm potentially impends even before an injury has established, pain may be regarded as the best accomplished and most vital mammalian sense, at all.

Within the last ten years several transducer molecules have been identified and characterized that are particularly activated by those tissue damaging stimuli in a direct or indirect manner. These membrane channels may alone or in concert with others specifically activate the peripheral pain sensing neurons. The most prominent of those is the so-called capsaicin-receptor TRPV1 that is directly activated by noxious heat and by several chemicals including capsaicin, the hot ingredient of chili peppers. TRPV1 is also activated and/or sensitized by numerous other chemicals, including several endogenous mediators that promote inflammation. In that context sensitization of a peripheral nociceptor facilitates its activation and ultimately lead to an activation of the pain sensing neuron by the non-noxious body temperature. Thus, this channels properties do explain why spicy food is perceived as being hot and it represents a molecular basis for the effectiveness of ice packs against inflammatory pain. Another interesting example is the membrane channel TRPM8 which is activated by cold temperatures and by menthol and thus may resemble the molecular basis for the cooling sensation induced by sweets containing peppermint. These membrane channels - that are directly activated by noxious stimuli or that integrate peripherally processing of the resulting nervous activation and convey these information to the central nervous system - are very attractive targets for a rational and purposive pain therapy.

However, in contrast to nociception, pain is unquestionably not only a sensation in parts of the body, but it is an unpleasant conscious emotional experience. Therefore, pain

reflects always a psychological state and is a subjective experience individually emerging from higher integrative processing within the subjects brain. The subjectively experienced pain results from the actual processing within the brain were its characteristics are affected by several components including emotional, cognitive, vegetative states and individual memories. Unfortunately, many people report pain in the absence of tissue damage or any likely pathophysiological cause or still long times after an injury had taken place which physically seemed to be completely cured. In these patients pain has lost its physiological warning function but has become a disease of clinical significance, itself. Similarly, in several incurable diseases pain may become the dominant symptom. Persistent or perseverative pain lasting longer than 6 month is defined as chronic pain.

Several mechanisms might contribute to the development of chronic pain. Information concerning painful stimuli is processed within the nervous system in the periphery, at the spinal cord level when entering the central nervous system as well as in several specific nociceptive circuits within the brain. At all these stages of neural processing, there are mechanisms involved that may contribute to amplification and/or attenuation of pain signalling. These mechanisms may enable the organism to adequately react to painful stimuli acutely as well as when painful stimuli occur for longer periods. The latter is thought to contribute to a phenomenon which is sometimes called “pain memory”. In other words, acute pain may persistently affect neural processing of subsequent painful stimuli, an effect which may outlast the injury for a long time. Thus, those principally reasonable mechanisms are a mixed blessing. Such an amplification of information concerning tissue damaging may ultimately lead to a self-adjusting and sustentative activation of the nociceptive system and therefore induce chronic pain independent of an injury by plastic changes of the system itself.

Furthermore, the pain processing system may itself be subject of pathological alterations that induce pain syndromes either acutely or chronically. Neuropathic pain is caused by primary lesions or dysfunctions within the nervous system. Examples are nerve injuries like the phantom-limb syndrome in course of amputation of extremities as an extreme form, central pain after cerebral apoplexies, infectious diseases directly inflaming the nervous system like herpes zoster, multiple sclerosis, etc., polyneuropathies in course of diabetes mellitus or alcohol abuse and several others.

In course of some psychosomatic disorders patients may, however, report severe pain but absolutely no –organic - impairment may be identified even after careful and detailed examination of the patient; this usually happens for psychological reasons. Normally there is no way to distinguish these patients experience from that due to tissue damage regarding the subjective report and- according to the IASP-definition – this is of course pain, too. Therapy of those patients may, however, be difficult when lacking a somatic basis of the disease. In that context pain is meanwhile regarded as a result from complex interactions integrating somatic, behavioural, cognitive and affective components within an individual. As a consequence multidisciplinary approaches are preferable to treat those patients adequately including physicians of different medical disciplines, psychologists and physiotherapists.

However, pain does not only amplify itself, there are also several – endogenous – mechanisms leading to a reduction of pain, like the endogenous opiate system. These mechanisms are also of high evolutionary relevance since they provide the capacity to act in extreme emergencies. Studying those mechanisms may also uncover attractive new targets for the treatment of pain in future.

Pain and especially chronic pain is an enormous problem for health care policies and presumably the most common disease leading to medical attendance in central Europe. More than 90 % of all Germans report that they have had pain during the preceding year. About one third of the German patients visiting a general practitioner suffer from chronic pain. Approximately each tenth inhabitant of Germany is thought to suffer from chronic pain and about the same percentage of Germans currently report to suffer from severe pain. About 40 % of all Germans are estimated to- at least periodically - suffer from lower back pain. About 30 % of all have recurrent tension type headache – each tenth with chronic progression, 10 % suffer from migraine. Pain is also a marked problem of aging societies since it further aggravates in older persons. About 40 % of all older Germans living at home and about 70 % of those living in foster homes suffer at least intermittently from pain. Symptoms such as depression and anxiety, sleep disturbances, weight loss and cognitive impairment may be related to pain or even be a manifestation of pain in older persons. Conversely, behaviours such as guarding, agitation, facial expression and altered mobility could in fact represent pain, for example, in Alzheimer's disease. Similar considerations apply to pain in neonates and infants.

Beyond the individual impairment and harm resulting from chronic pain costs of several billion dollars have to be covered by the public health system for stoppage, therapy, rehabilitation or retirement. Unfortunately, the fundamental treatment options for pain have - in principal - not changed within the last centuries using extracts of opium poppy or from willow bark in more or less unmodified preparations until recently. Therefore, from ethical, social as well as economical considerations it is urgently essential to improve our knowledge on pain.

Several improvements have been made within the last years in basic pain research regarding molecular fundamentals of the genesis of pain using molecular-biological techniques together with functional characterization such as electrophysiology and several imaging techniques *in vitro*. Numerous morphological and/or functional processes were identified that are initiated by the different aspects of pain and that lead to a modified pain processing within the nervous system. Functional neuroimaging techniques and neurophysiological methods *in vivo* increasingly identify and characterize areas and processes within the central nervous system activated by the different aspects of the emotional experience pain. Several new methods were established that make the subjective pain experience measurable which thus enable clinical studies and worldwide comparison of the results.

Combining this enormous growth in knowledge of molecular, cellular and systemic mechanisms underlying nociception and pain will have important implications for the clinical diagnosis and therapy of pain syndromes. A challenge for the near future will be to transfer those basic research results from the laboratories into the clinics for the welfare of pain suffering patients. A further milestone will be to establish a mechanism based classification of pain that separates different causes - such as peripheral or central sensitization of the nociceptive system – and may ultimately lead to a mechanism based rational pain therapy. The next decade will doubtlessly lead to increasing knowledge of development, progression and maintenance of pain as well as of its specific therapy by multidisciplinary research done in co-operation by clinicians and basic researchers that are encouraged by a conclusion made by Galenos from Pergamon already 2000 years ago: "Divinum est sedare dolorem" – "It is a divine challenge to alleviate pain".