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Brain electrical correlates of pain processing

Hirnelektrische Korrelate der Schmerzverarbeitung

Summary Pain is the result of complex neuronal activities within the brain and not simply the result of peripheral activities of the nociceptive system. Pain results from an interaction of many neuronal modules located in different brain areas. This interaction is modified by anticipation, learning, and perception. Electrophysiological phenomena allow the characterization of the information processings associated with pain. This characterization is important for theoretical purposes and for the evaluation of different therapeutic strategies. Furthermore, electrophysiological phenomena support the investigation of functional plasticity in the brain as one of the consequences of chronic pain processing. It is expected that new methods of cortical source analysis will contribute considerably to our understanding of different aspects of pain processing and of the management of pain.

Zusammenfassung Schmerz ist das komplizierte Resultat verschiedener neuronaler Aktivitäten unseres Gehirns und nicht nur ein einfaches Ergebnis der Tätigkeit des peripheren nozizeptiven Systems. Schmerz resultiert aus dem Zusammenspiel verschiedener Module im Gehirn, die sich in verschiedenen Hirnarealen befinden und durch Erwartung, Lernen, Erfahrung und ähnliches modifiziert werden. Elektrophysiologische Begleiterscheinungen, die mit der Schmerzverarbeitung assoziiert sind, erlauben dabei eine Charakterisierung der ablaufenden Informationsverarbeitungsprozesse. Neben der grundlagentheoretischen Bedeutung spielt hier die Evaluation verschiedener Therapieansätze eine herausragende Rolle. Zusätzlich können mittels der Registrierung hirnelektrischer Prozesse Vorgänge der funktionellen Plastizität im Zusammenhang mit der Schmerzverarbeitung untersucht werden. Neue quellenanalytische Ansätze lassen dabei einen deutlichen Erkenntnisgewinn über die Rolle einzelner Hirnstrukturen bei der Verarbeitung und Behandlung von Schmerzen erwarten.

Key words Pain – event-related potentials (ERP) – central nervous system (cns) – functional plasticity

Schlüsselwörter Schmerz – ereigniskorrelierte Potentiale (EKP) – Zentralnervensystem (ZNS) – funktionelle Plastizität

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Introduction

In the past pain research was mainly concerned with the characterization of nociception, i.e., with the question how noxious stimuli are processed in order to perceive pain. There is no doubt that important knowledge has been achieved in theoretical and clinical terms. Nociception consists of transduction and transformation, sensitivation, processing of noxious stimulus properties into a neural language that the central nervous system is able to process properly and of processes within the physiological structures of the periphery and the central nervous system. These processes constitute the primary neurophysiological basis of pain. The nociceptive system represents a simple structured, inherent warning system, which signals tissue lesions, infections, and

other modifications of the skin and connective tissue structures. Classic pain concepts assumed that pain sensation is a direct consequence of the extent of peripheral nerve activation. However, recent studies doubt this rather rigid formulation and suggested the "Gate Control Theory of Pain" presented by Melzack and Wall (30). After several transformations (28, 29) this theory emphasizes that only the result of central information processing determines the phenomenon of pain. Thus, pain goes far beyond nociception in so far as experience, learning, emotional activities, and aspects of subjective coping are involved in the processing of nociceptive information that all act as modulators and add to the question how we finally experience pain. These processes can at least partially be independent of nociception (27, 33). These considerations are supposed to have significant clinical consequences: pain should be defined as a private experience, the significance of which depends on our previous individual experience, our socio-cultural learning activities, the present degree of attention or distraction and on memory functions, and our abilities to control our pain experience.

Pain processing in the central nervous system

The experience of pain is mediated by the activity of different cortical and subcortical structures. By means of Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) it has been shown that several spatially distributed cortical and subcortical areas participate in the nociceptive processing and pain (9, 10, 38, 42). Besides the primary and secondary somatosensory cortical areas, the prefrontal cortex, anterior parts of the gyrus cinguli, parts of the thalamus, the nucleus lenticularis in the cerebelum, the periaquaductal grey, and the insula, all are involved in the processing of nociceptive events (9, 10, 38, 42). Somatosensory cortical fields and parts of the thalamus are believed to be the basic structures for the processing of somatosensory features (i.e., localization, strength). Structures of the upper prefrontal cortex, medial parts of the thalamus, and the cingular cortex are considered to intergrate the affective component of pain processing (42). According to the modular organization of the brain, which reflects a basic assumption in neuroscience, spatially and temporally organized communications between different moduls of these brain regions are considered to be of great importance for normal pain processing (37).

The quality and the intensity of pain experience depend on synchronized activities of different neuronal brain moduls. Their activities should temporarilly be correlated with each other. For such organized systems Pöppel et al. (35–37) suggested that the different moduls should be activated in a time period of about 25 ms. Indeed, numerous studies concerning the communication between different brain areas indicate an oscillatory frequency of about 40 Hz, called gamma-activity (17, 40, 41).

Bioelectrical phenomena in pain processing

By means of PET and fMRI it has been shown which brain structures are involved in pain processing. Since the temporal resolution of these methods is restricted to minutes or seconds, these methods can not properly discover coherent relations between cortical structures involved in pain processing. Bioelectrical and biomagnetic methods, however, have a temporal resolution of milliseconds. Therefore, such methods could contribute to our understanding of the temporal involvement of different structures of the brain into the processing of pain. Present findings mainly come from three subgroups of investigation:

- from studies on spontaneous changes in the electroencephalogram (EEG) and magnetoencephalography (MEG) during pain processing,
- from studies on event-related changes to painful stimuli during normal pain processing or during the quantification of analgesic agents, and
- from studies on neuronal sources subserving the processing of pain.

Studies on the spontaneous changes in the EEG and MEG during pain processing

Based on the assumption, that the EEG reflects excitation and inhibition of different neuronal moduls, changes in the cortical power spectrum can be interpreted as measures how these structures are involved in the processing of pain. It has been shown that during pain modifications occur in almost all classical EEG frequency bands (5, 6, 16). An increase of power within the beta-frequency band as well as in higher frequency bands has been reported during pain. At the same time, a decrease was found in the alpha-frequency range. Additionally, there are studies demonstrating modulations of the EEG power spectrum due to the administration of different analgesics. As a rule, a decrease of alpha activity combined with a significant increase of slow activities in the delta-range was found during analgesia as compared to placebo (3, 5, 6). Recent findings about changes in the coherence spectrum between different brain areas, showing an increase of oscillatory coherence in the 40 Hz range during pain processing are of particular interest (1, Miltner et al., submitted).

Event-related potentials in pain and during quantification of analgesic influences

Apart from frequency modifications of the spontaneous EEG, somatosensory event-related potentials (SEP) and somatosensory event-related magnetic fields (SEF) were used to quantify how subjects perceive the intensity and quality of somatosensory stimuli as well as to value analgesic substances. In this field of EEG research subjects or patients are stimulated painfully. Brain potentials or fields to these stimuli are recorded from different sites of the brain and then averaged. In the SEP or SEF different components can be identified, which are defined by their latencies. Thus, the P100-component means a component of the brain potential, which shows its maximal positive amplitude 100 ms after a painful stimulus. Irrespective of the stimulus modality, a positive relation between stimulus intensity and report on the intensity of the subjectively experienced stimulus has been shown where different components of SEP and SEF have been qualified as brain electrical correlates of pain processing in humans (7, 8, 13, 14, 31, 32, 44). It was shown that the amplitudes of the SEP components correlate considerably more with the subjective pain report than with the physical stimulus intensity (12, 31). Therefore, electrocortical activities are assumed to be a useful parameter for the investigation of cortical processes of pain perception and the impact of pain treatment methods.

Different studies examined SEP and SEF to painful stimuli in healthy controls and different groups of chronic pain patients (3, 18, 25, 44). It has been established that there is a clear difference in processing of painful stimuli between chronic patients and healthy controls, e.g., patients with chronic back pain show no significant differences in the SEP amplitudes when stimulated on the back (Bauder & Miltner, submitted). These patients react with higher SEF power as compared to healthy subjects (18). Furthermore, SEP and SEF can be used to examine the influence of analgesic drugs. First studies concerning the influence of peripheral analgesics on SEP induced by noxious stimulation were presented by Chen and Chapman (15). Their experiments have shown that a highly significant reduction of different SEP amplitudes occurs after application of acetylsalicylic acid. Analgesics affect more or less all potential components. The above mentioned results have been replicated several times. Furthermore, other peripherally effective analgesics seem to give similar effects (26). In recent years numerous analgesics which act on the central nervous system were tested concerning their influence on nociceptive evoked potentials and fields. This analysis refers to opiates, opiate derivates, and numerous non-narcotic analgesics as well as antidepressants (5, 6, 11). Accordingly, results show a reduction of amplitudes as well as a clear prolongation of corresponding latencies in the range of 100-400 ms post-stimulus during analgesia. This reduction of amplitude is accompanied by a significant decrease of subjective pain reports. SEP and SEF have been also used to assess the power of psychological pain control methods such as distraction of attention and hypnosis. During the distraction of attention from the painful stimulation subjects experienced pain stimuli as less painful which correlates with a decrease in the late SEP components (23, 34). Furthermore, in hypnosis late components of SEP do not indicate any differences between baseline condition, hypo- and hyperalgetic conditions (33). However, during suggestions aimed to increase the experience of pain significantly higher ratings about the experienced pain were found than during a suggestion applied to decrease the pain experience. Subjective decrease of pain has been experienced although there was no change in stimulus intensity. These and other experiments on the influence of hypnosis on SEP and SEF amplitudes have led to different hypotheses. It is clear from these studies that stimuli applied during hypnosis are processed by the cortex without any modification, whereas information processes that follow the first evaluation of stimuli result in a reassessment of the pain sensation. A dissociation between neuronal moduls responsible for pure somatosensory processing and those evaluating the painful stimuli represents one possible interpretation (22, 31).

Neuronal source analysis in pain processing

Event-related fields and potentials are used to model neural generators of these fields and potentials. Hari et al. (20, 21) presented the first MEG studies about the localization of neuronal structures that might be involved in the processing of pain, experimentally induced by electrical tooth pulp stimulation or electrical finger stimulation. Besides neural activities in the secondary somatosensory areas these stimulations cause neural activities in the primary somatosensory cortex contralateral to the side stimulated (24, 25). Furthermore, magnetic field activities can be localized in a time period of about 250 ms post stimulus localized in both secondary somatosensory brain areas and in the anterior cingulate. Sources of neuronal activity can be found not only by means of MEG, but also with SEP to painful stimulation. For example, Tarkka and Treede (43) were able to identify neural sources of electrocortical activities after laser-heat stimulation in the representative areas of the stimulated hand, i.e., in the primary somatosensory cortex contralateral to the stimulation side, in both secondary somatosensory cortices bilaterally and in the anterior cingular cortex. To summarize, these data show good correspondence of results of most investigations (4, 43) that also correspond to the studies

using fMRI or PET (9, 10, 38, 42). From all these studies it is now pretty clear that the processing of painful stimuli is performed in primary (SI) and secondary areas (SII) of the somatosensory system. It is assumed that SI is involved in the analysis of the stimulus localization and SII in the analysis of the sensory characteristics. Parallel to these processes, but with longer duration, the emotional qualities of pain experience are evaluated in subcortical limbic and paralimbic brain structures.

Plasticity in the pain processing system

The working capacity of the nociceptive system and the brain is not rigid or fixed. This system can be modulated continuously whenever pain is processed. It can become modulated by learning processes and by other types of psychological influences. Such modifications can be seen at all levels of the brain. Thus, studies performed during long-lasting painful stimulation indicate that significant more receptors are exprimed and so-called sleeping neurons are evoked already at the spinal level (39). This kind of experience-related plasticity is important for the development and maintenence of chronic pain, because the increased sensitivity will amplify neural activities to peripheral stimulations. Our own data and those of Flor and Birbaumer show that activities of larger neuronal moduls in the somatosensory cortex undergo plastic modifications during chronic pain (2, 18, 19, 45). In a study with patients after finger amputation suffering from phantom pain we have found that the receptive field structure of the amputated finger rapidly changes. It was demonstrated that the SI deafferented after amputation became occupied by neighbouring areas, i.e., by cortical areas that serve the neighbouring fingers (45). Similar modifications were observed after amputations of an upper extremity. The observations in phantom pain patients indicate, that pain can occur completely without any nociceptive input from the peripheral structures into the brain. These studies clearly support our notion that the brain is the central organ of pain sensation and perception.

Conclusions

Pain is the complex result of many different neuronal activities which take place in peripheral structures and in our brain. Therefore, pain cannot be understood as a result of simple processes of the peripheral nociceptive system alone. Pain results from complex interactions between different brain moduls, which are itself modified by anticipation, learning processes, coping processes, etc. The electrophysiological phenomena associated with pain processing allow an excellent characterization of the ongoing information processes in different structures of the brain. New techniques of source analysis of brain structures involved in the experience of pain are expected to produce valuable knowledge about mechanisms of how different therapies modify the experience of acute and chronic pain.

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