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Basal opioid receptor binding is associated with differences in sensory perception in healthy human subjects: A [^{18}F]diprenorphine PET study

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ABSTRACT

The endogenous opioid system is involved in many body functions including pain processing and analgesia. To determine the role of basal opioid receptor availability in the brain in pain perception, twenty-three healthy subjects underwent positron emission tomography (PET) utilizing the subtype-nonselective opioid antagonist [^{18}F]diprenorphine, quantitative sensory testing (QST) and the cold pressor test. Binding potentials (BPs) were calculated using a non-invasive reference tissue model and statistical parametric mapping was applied for *t*-statistical analysis on a voxelwise basis. We found that cold pain-sensitive subjects present a significantly lower BP in regions including the bilateral insular cortex and the left orbitofrontal cortex. In addition, correlation analysis revealed an inverse correlation between opioid BP in the bilateral motor and premotor region and perceptual wind-up. These findings indicate that interindividual differences in pain perception are partially accounted for by basal opioid receptor availability.

A secondary aim of this study was to investigate the contribution of basal opioid receptor availability to the perception of non-nociceptive stimuli. The following negative correlations between regional opioid BP and scores of QST parameters were found: BP in the right premotor cortex and scores of alternating cold and warm stimuli, BP in the left midcingular cortex and scores of cold detection threshold, BP in the left insula and scores of mechanical detection threshold. These results suggest that the opioid receptor system is involved in the perception not only of pain but also of non-painful somatosensory stimuli.

Introduction

Human brain activity involved in the perception of thermal and mechanical stimuli has been demonstrated by previous imaging studies (reviewed in Treede et al., 1999; Porro et al., 2004). Consequently, a cortical and subcortical network including sensory, limbic, associative and motor areas has been identified over the last decade. In terms of pain, further concepts of functional specialization have emerged. Based on differences in thalamic projections, neuronal organisation and function, the cortical nociceptive network has been divided into a lateral and medial system (Treede et al., 1999). The lateral system includes the primary and secondary somatosensory cortex and is thought to encode for sensory-discriminative features (e.g. localization and duration of pain) (Chudler et al., 1990; Kenshalo and Isensee, 1983; Kenshalo et al., 1988). On the contrary, structures of the medial system such as the anterior cingulate and insular cortex (ACC, IC) belong to the limbic system (Papez, 1937) and are most likely involved in processing affective and motivational components of pain (Rainville et al., 1997; Tölle et al., 1999; Schreckenberger et al., 2005).

The endogenous opioid system strongly attenuates the perception of pain. The most common clinical use of opioids is for analgesic effects, which are mainly transmitted by μ-opioid receptors on a spinal and supraspinal level. However, the analgesic effect can also be modulated by endogenous ligands. Endogenous opioid peptides (EOP) are known to be released under pain stimulation, followed by an increase in opioid receptor occupation and an analgesic effect. Receptors are widely distributed in the human brain including important structures of the nociceptive system such as periaquaeductal grey (PAG), thalamus, ACC and IC (Jones et al., 1991; Benchérif et al., 2002; Baumgärtner et al., 2006).

Nowadays, it is possible to image these opioid receptors in vivo using the technique of ligand-positron emission tomography (PET)

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(reviewed in Henriksen and Willoch, 2008). By labelling an opioid with a positron emitting radioisotope (normally [^{11}C]-carfentanil, [^{11}C]-, or [^{18}F]-diprenorphine), the technique provides a unique method to quantitatively measure opioid receptor availability. Utilizing ligand-PET, different laboratories have found changes in opioid binding potential (BP) in healthy subjects undergoing acute painful stimulation (Zubieta et al., 2001, 2002; Bencherif et al., 2002; Scott et al., 2007). In addition, an alteration of opioid BP in patients presenting chronic pain was described over the last two decades (Jones et al., 1994, 1999, 2004; Willoch et al., 2004; Sprenger et al., 2006a; Maarrawi et al., 2007b). Irrespective of the different study designs, the results demonstrated a decrease in opioid receptor availability. In particular in respect to acute painful stimulation, this modification was most commonly interpreted as an activation of the opioid receptor system due to EOP release.

Previous ligand-PET studies have focused on alterations of opioid receptor availability under acute pain stimulation or in patients with a history of chronic pain. In contrast, the functional relationship between basal opioid receptor availability prior to stimulation and the perception of a painful stimulus has not been investigated so far. Our objective was therefore to evaluate the correlation of basal opioid receptor availability and the experience of painful stimulation in healthy subjects using the technique of ligand-PET. A secondary goal was to investigate possible correlations between basal opioid receptor availability and non-nociceptive somatosensory perception. To avoid influences of gender in opioid neurotransmission and somatosensation as was shown elsewhere (Zubieta et al., 1999, 2002; Sarlani et al., 2003; Kim et al., 2004; Rolke et al., 2006a) we only included male subjects in this study.

Methods

This study was carried out in accordance with the Helsinki Declaration and was approved by the local ethics committee, the Federal Health Administration (BFArM) and the German radiation protection authorities (BfS).

Subjects

Twenty-three healthy male volunteers (age 23–51 years, mean = 30 years) were included in this study and were paid for participation. The subjects had no previous history of relevant physical illness, no current or past psychiatric disorders, no family history of major psychiatric disorder in first-degree relatives, and they were not taking medication regularly. All subjects received a mental and physical state examination including blood analyses and drug screening. Informed written consent was obtained from each subject.

Quantitative sensory testing and cold pressure test

A somatosensory profile of all volunteers (quantitative sensory testing, QST) was assessed using the comprehensive protocol of the German research network on neuropathic pain (DFNS) published by Rolke et al. (2006b). QST is a standardized test battery which consists of seven tests measuring 13 parameters:

- thermal detection thresholds for the detection of cold (cold detection threshold, CDT), warm (warm detection threshold, WDT), alternating cold and warm (thermal sensory limen procedure, TSL) and paradoxical heat sensations (PHS),
- thermal pain thresholds for cold (cold pain threshold, CPT) and hot stimuli (heat pain threshold, HPT),
- mechanical detection thresholds for touch (mechanical detection threshold, MDT) and vibration (vibration detection threshold, VDT),
- mechanical pain sensitivity including thresholds for pinprick (mechanical pain threshold, MPT) and blunt pressure (pressure pain threshold, PPT), a stimulus–response function for pinprick sensitivity and dynamic mechanical allodynia (mechanical pain sensitivity, MPS, allodynia to light touch, ALL), and pain summation to repetitive pinprick stimuli (wind-up ratio, WUR).

QST assesses the quantity of somatosensory functions of both physiological and pathophysiological sensations, e.g. allodynia (ALL) or paradoxical heat sensations (PHS). As such a gain of function can by definition not be detected in healthy volunteers, the parameters ALL and PHS were not considered in this study. Furthermore the scores of vibration detection threshold (VDT) do not scatter in healthy human subjects, since nearly all subjects detect vibration until 8/8 of the Rydel–Seiffer tuning fork. Consequently, the parameter VDT is not qualified for correlation analysis.

QST data were assessed as raw values or log values according to Rolke et al. (2006b). High scores in nociceptive and non-nociceptive detection thresholds (CDT, WDT, TSL, CPT, HPT, MDT, MPT, and PPT) indicate low somatosensory perception sensitivity, while high scores in mechanical pain sensitivity (MPS) and wind-up ratio (WUR) represent high or enhanced pain perception sensitivity respectively.

In addition to QST, the sensitivity to cold pain was determined using a cold pressor test. Ice water of <1 °C was prepared and the subjects had to immerse their right hand up to the wrist for a maximum of 180 s. Actual pain was rated on a 0–100 numerical rating scale (NRS) every 10 s. Zero, the lower anchor point, represented “no pain”; 100, the upper anchor point, represented “the most intense pain imaginable.” Furthermore, the time until withdrawal when pain became unbearable was recorded. In these cases, the maximum NRS value of 100 was extrapolated for the whole 3 min period (last observation carried forward). Depending on whether cold-induced pain exceeded a value of 95 NRS during 180 s of ice water exposure or not, individuals were classified as “cold pain-sensitive” or “cold pain-insensitive.” We used this cut-off because several highly motivated subjects left their hand in ice water in spite of a pain intensity very close to 100 NRS. All stimuli were applied to the right hand of the subjects.

Radiochemistry

The synthesis of [^{18}F]fluoroethyl-diprenorphine ([^{18}F]DPN) was achieved applying the secondary labelling precursor 2-[F-18]fluoroethyltosylate to 3-*O*-trityl-6-*O*-desmethyl-diprenorphine (TDD) (Wester et al., 2000). The 2-[F-18]fluoroethyltosylate was synthesized as described elsewhere (Wängler et al., 2004) and obtained in a diethyl ether solution which was evaporated in a stream of nitrogen. To the dried 2-[F-18]fluoroethyltosylate a solution of 4 mg TDD and 10 mg sodium hydride in 300 µL of DMF were added and the resulting mixture was stirred for 8 min at 100 °C. The reaction mixture was cooled to room temperature, 600 µL HCl (2N) were added slowly and stirred for 5 min at 40 °C. After the mixture was cooled to room temperature it was diluted with 8 mL aqueous ammonia (20 %), stirred for 2 min, and loaded on a Sep-Pak C-18-cartridge. The product was eluted with 2 mL of methanol and purified using semipreparative HPLC (µBondapack C_{18}, 300 × 7.8 mm inner diameter, acetonitrile/0.1N ammonium formate 55:45, 3 mL/min, tr: 14.9 min). After diluting the HPLC fraction containing the product with 40 mL 0.1N ammonium formate, it was loaded on a Sep-Pak C-18-cartridge, washed with 10 mL water, eluted with 1 mL ethanol and diluted with 9 mL physiological saline solution to yield 1250–1950 MBq (RCY 19 ± 4 %) of [^{18}F]DPN. HPLC analysis (Luna 5 µm, C18(2), 250 × 4.6 mm inner diameter, methanol/0.1N ammonium formate 70:30, 1 mL/min, tr: 12.2 min) showed that the radiochemical purity was >99%, while the specific activity (determined via UV–calibration curve) was between 580 and 820 GBq/mmol.