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Evidence for endogenous opioid release in the amygdala during positive emotion

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ABSTRACT

Endogenous opioid release has been linked to relief from aversive emotional memories, thereby promoting a euphoric state and subsequent interactions towards social stimuli resulting in the formation of social preferences. However, this theory remains controversial. Using positron emission tomography and [^{11}C] diprenorphine (DPN) in healthy volunteers, we found significantly reduced DPN binding to opioid receptor in the hippocampus during positive mood induction compared to neutral mood. Furthermore, the magnitude of positive mood change correlated negatively with DPN binding in the amygdala bilaterally. Our finding of reduced DPN binding is consistent with increased release of endogenous opioids, providing direct evidence that localised release of endogenous opioids is involved in the regulation of positive emotion in humans.

Introduction

Opioid peptides act as mediators of use-dependent synaptic activity modulating the effect of fast-acting primary neurotransmitters, such as glutamate and dopamine (Snyder and Pasternak, 2003). In a number of species, the opioid system has been linked to the rewarding (pleasurable) effects of a variety of behaviours: affiliative behaviours (Panksepp et al., 1980a; Matthes et al., 1996; Moles et al., 2004), pain relief (Quirarte et al., 1998; Fields, 2007; Leknes and Tracey, 2008), palatable food intake (Berridge, 1996; Will et al., 2004; Pecina, 2008), social play (Panksepp et al., 1980b; Panksepp and Bishop, 1981), sex (Agmo and Berenfeld, 1990; Paredes and Martinez, 2001), brain stimulation reward (Belluzzi and Stein, 1977; Trujillo et al., 1989) and heroin self-administration (Koob et al., 1989; Wise, 1989). Panksepp and others (Panksepp et al., 1980a,b; Panksepp et al., 1997) have provocatively argued that positive social stimuli elicit release of endogenous opioids, thereby promoting a euphoric state and subsequent interactions towards social stimuli resulting in the formation of social preferences.

In humans, studies that relate opioid neurotransmission to mood have so far been limited to pharmacological challenges (Preston and Bigelow, 1993) and post-mortem studies in suicide victims (Gabilondo et al., 1995). These studies reported increased numbers of opioid receptors or opioid radioligand binding and suggested an adaptive response of the postsynaptic receptors to altered levels of presynaptically released endogenous opioids. A recent PET study unexpectedly found increased binding of the μ-opioid receptor agonist ^{11}C-carfentanil during a sustained sadness state compared to a neutral state in healthy controls, which was interpreted as deactivation of neurotransmitter release (Zubieta et al., 2003). In contrast, decreased ^{11}C-carfentanil during sustained sadness was observed in the insular cortex, amygdala and thalamus of patients with major depressive disorders (Kennedy et al., 2006).

The binding of the radioligand [^{11}C]diprenorphine (DPN) to mu, kappa, and delta opioid receptors can be altered by pain stimulation (Jones et al., 1999) and seizure activity (Bartenstein et al., 1993; Koepp et al., 1998, Hammers et al., 2007a) and is thus considered to be sensitive to the release of endogenous opioids. Here we demonstrate, consistent with Panksepp's hypothesis, that experience of positive emotions is associated with decreased amygdala activity modulated through increased opioid-related inhibition.

Materials and methods

Participants

Twenty-five healthy right-handed volunteers (18 males) with a median age of 36 years (range: 30–52 years), without a history of psychiatric or neurological disease took part in the study, which was approved by the Hammersmith Hospital Ethics Committee and Administration of Radioactive Substances Advisory Committee. Informed consent was obtained for all participants after procedures

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were fully explained. All experiments were conducted according to the principles expressed in the Declaration of Helsinki.

PET scan acquisition

Ten participants (seven males) received two [^{11}C]diprenorphine (DPN) PET scans, one during a positive mood induction procedure and one during a neutral mood induction procedure. Another fifteen participants received two [^{11}C]DPN PET scans without mood induction procedures to test the reliability of our measurements. PET scans were obtained using a Siemens/CTI PET camera operated in 3D mode on separate days (median 3 days apart). Participants received a total dose of 260–370 MBq [^{11}C]DPN. Continuously sampled and additional discrete samples were taken in order to derive a metabolite corrected arterial input function. In one individual (participant 4), the arterial line necessary for quantifying DPN binding clotted after 5 min of the second scan, thus paired data could only be analysed for nine of these ten subjects. Emission data was acquired in list-mode over 90 min covering an axial field of view of 21.5 cm, and then re-sampled into 32 frames of increasing duration designed to cover optimally the area under the head curve. Head movement during scanning was minimised by the use of a moulded headrest and external head markings aligned to fixed laser lights every 5 min. The reconstructed image resolution for 95 simultaneously acquired planes was about 4.8×4.8×5.6 mm at full width at half-maximum. Voxel-by-voxel parametric images of [^{11}C]DPN volume of distribution (DPN-Vd), reflecting [^{11}C]DPN binding to μκ and δ-opioid receptors, were produced from the time courses of brain uptake and the arterial plasma input functions using spectral analysis (Cunningham and Jones, 1993; Hammers et al., 2007b).

Mood induction procedure

The mood induction procedures started 20 min before injection of [^{11}C]DPN with a 10-minute video-clip of the simulated orgasm scene (positive condition) in the movie *When Harry Met Sally* (1989; Director: Rob Reiner; Writer: Nora Ephron, Studio: MGM) or for the neutral condition a nature movie "*Realms of the Russian Bear*" (1992; BBC Television). This was followed by participants listening to their own choice of favourite music (positive condition) or a recording of classical music (neutral condition) in the background for the rest of the investigation. From 10 min before the radiotracer injection until the end of the scanning period, the participants read either positive Velten statements (such as "there are so many good things in my life, I really feel lucky") or neutral statements, adapted for British volunteers (such as "Birmingham is a large city") (Bench et al., 1992) The Velten Statements were presented for 30 s each on a video screen and participants were instructed to read the statements silently and to get into the appropriate mood. This was supplemented during the positive mood induction procedure by an unexpected gift of £30 (Baker et al., 1997) at the time of injection; the banknotes remained visible throughout the scan. The order of conditions was counterbalanced amongst subjects.

Positive and negative affect inductions are not usually symmetrical or parallel in their effects, with positive mood inductions affecting positive, but not necessarily negative affect. We therefore chose the difference in positive affect scales (PAS) as an indicator for the magnitude of positive mood shift during the two conditions (neutral and positive). Participants were also asked to assess their mood on visual analogue scales (VAS) from 1 to 10 for happiness, sadness, amusement, pain and interest at various time intervals prior to and following injection of the radiotracer. We used a composite score of happiness and amusement to best describe positive mood aspects, and calculated the difference between mean self-assessment at 15, 30 and 60 min post-injection and self-assessment prior to injection, with positive values suggesting a positive change in mood.

We used the difference in positive affect scales (PAS) as an indicator for the magnitude of positive mood shift during the two conditions (neutral and positive).

Image analysis

We used Analyze AVW version 5.0 (Robb, 2001) to perform image manipulation and measurements. Parametric maps of [^{11}C]DPN-Vd were analysed using an automated volume-of-interest (VOI) approach (Hammers et al., 2003) and SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London) implemented in Matlab 5 (Mathworks, Sherborn, MA). Firstly, a [^{11}C]DPN-Vd template in MNI/ICBM152 space was created using co-registered MRIs in SPM2. For voxel-based SPM analysis, individual [^{11}C]DPN-Vd images were stereotactically normalised to the [^{11}C]DPN-Vd template and smoothed using a 10 mm Gaussian kernel. Predetermined contrasts of the condition effects at each voxel were assessed using the usual *t*-statistic, giving a statistical image for each contrast. For the VOI analysis, the inverse of the spatial normalisation parameters was used to spatially back-transform a probabilistic anatomical atlas in MNI/ICBM space (Hammers et al., 2003) onto the individual [^{11}C]DPN-Vd images, using the Deformations Toolbox within SPM.

Results and discussion

The goal of our experiment was firstly to show that a positive shift in mood is associated with decreased cerebral [^{11}C]DPN binding, and secondly that this effect is most pronounced in regions with an especially high density of opioid receptors (Lewis et al., 1981). Differences in [^{11}C]DPN binding between a positive or neutral mood induction procedure were used to infer mood-induced changes in cerebral opioid receptor availability.

Behavioural measurements

Effect of mood induction

Using the brief positive and negative affect scales (PANAS) (Watson et al., 1988) we assessed mood during positive and neutral mood conditions, before the start of the mood induction procedure (baseline), and again 20 min after injection of [^{11}C]DPN. In one participant, PET data was irretrievably lost during the second PET scan due to arterial line failure, and this individual was excluded from the analysis. Seven of the nine remaining participants showed marked differences in their mood evaluation during the two scans. Subjects' ratings of mood change during the positive (ΔVAS happiness/amused: 3.2; range: −1.7 to +7) and neutral conditions (ΔVAS happiness/amused: −2.7; range: −7 to +0.7) were consistent with the intended valence ($p<0.05$). The mood induction procedure had no consistent effect on negative affect or arousal.

We maximised the mood induction effect by choosing a combination of stimuli that were effective in previous studies. These included watching a video-clip, listening to background music and reading Velten statements (Velten, 1968). This was supplemented during the positive mood induction procedure by an unexpected gift of £30 at the time of injection. The video-clip (the simulated orgasm scene in the movie "*When Harry Met Sally*" 1989. Film. Directed by Rob Reiner. USA: MGM) induced the target emotion of "amusement" in 93% of 72 American undergraduates (Gross and Levenson, 1995) and, in another study, unexpected gifts were the second most effective (83%) after watching a film (100%) in inducing an elated mood (Gerrards-Hesse et al., 1994).