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ORIGINAL INVESTIGATION

Emotional perception modulated by an opioid and a cholecystokinin agonist

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Abstract
Rationale The cholecystokinin (CCK) and opioid neuromodulatory systems work in an antagonistic fashion and can modulate emotional states and noxious input in opposite directions. In this behavioral study, we generalize this idea and suggest that CCK and opioids can modulate the processing of other external signals, e.g., visual stimuli rather than only noxious input.
Objectives The objective of this study was to determine whether CCK and an opioid agonist could modulate the emotional experience of visual stimuli.
Materials and methods Thirteen healthy male volunteers viewed standardized pictures with either neutral or unpleasant content. Simultaneously, one of three treatments was administered in a randomized, double-blind crossover design: the CCK_b receptor agonist pentagastrin (0.1 μg/kg), the mu-opioid receptor agonist remifentanil (0.0625 μg/kg), or saline. Self-ratings of the emotional experience of pictures and drugs were sampled together with psychological tests and recording of heart rate.
Results Pentagastrin treatment increased the rating of unpleasantness for both neutral and unpleasant pictures, while it decreased the rating of pleasantness for the neutral pictures. These effects did not correlate with the degree of general unpleasantness induced by the drug. Remifentanil treatment increased the pleasantness for the neutral pictures. While pentagastrin treatment induced a heart rate increase, unpleasant pictures induced a heart rate decrease, and the magnitude of change in heart rate correlated positively for these conditions.
Conclusions This study shows that the CCK and the opioid system modulate how external stimuli are emotionally perceived, suggesting a possible involvement in affective disorders.

Keywords CCK · Opioid · Emotion · Autonomic response · Visual stimuli · Perception

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Introduction

Emotion and pain are both powerful regulators of behavior. However, subjective pain and emotional experiences are not directly related to sensory input. Instead, the response to a standard input is variable and depends on both the context and the internal state of the subject (Frith and Dolan 1997; Mesulam 1998). For example, it has been shown that top-down mechanisms can interact with both the processing and the experience of noxious (Colloca and Benedetti 2005; Melzack and Casey 1968; Petrovic et al. 2002; Sullivan et al. 2001; Turner et al. 2000) and emotional stimuli (Mobbs et al. 2006; Petrovic et al. 2005). Attentional processes such as distraction (Hodes et al. 1990; Petrovic et al. 2000), coping with aversive situations (Weisenberg 1998), and the placebo response (Colloca and Benedetti 2005) are all examples of top-down regulatory mechanisms of pain. Similar top-down mechanisms have been suggested for

emotional processes (Ochsner and Gross 2005). In affective disorders, emotionally negative input is often described as a disproportionally negative experience. While a marker for depression is anhedonia and negative views of all experiences, anxiety is often linked to increased specific fear processing for external stimuli (Sadock and Sadock 2003). Thus, studying how top-down control can change the emotional experience of external stimuli is important both for understanding affective disorders and developing new treatment strategies. In this study, we examined neuromodulation of emotional perception in healthy controls using pharmacological manipulations of systems believed to be involved in both cognitive control and affective disorders.

We have previously suggested that top-down cognitive control mechanisms may be effected by specific descending neuromodulatory systems to regulate ongoing possessing of pain (Petrovic et al. 2002) and emotions (Petrovic et al. 2005). One example of top-down modulation where the involved neuromodulatory system is partly known is placebo analgesia. This process activates the endogenous opioid system to suppress pain, as indicated by naloxone (an opioid receptor blocker) – induced attenuation of the placebo analgesic response (Colloca and Benedetti 2005; Levine et al. 1978). Similarly, the cholecystokinin (CCK) antagonist proglumide can reduce pain perception by interacting with expectation pathways and, thereby, enhancing the placebo analgesic response (Benedetti et al. 1995, 2006; Benedetti 1996). These studies emphasize the role of the CCK–opioid system in cognitive processing and indicate that they may act in antagonistic directions, in line with the findings that opioids act as analgesics and CCK agonists as anti-analgesics (Cesselin 1995; Fields and Basbaum 1999; Hebb et al. 2005).

Apart from the interaction with the regulation of pain, these top-down neuromodulatory systems seem to have a direct effect on mood (Hebb et al. 2005). For example, administration of opioids induces a sensation of pleasantness (Berridge 2003; Koob et al. 1989), contrary to CCK agonists that induce unpleasantness and anxiety (Bradwejn et al. 1991; Radu et al. 2002, 2003). In higher doses, administration of a CCK agonist induces panic attacks (de Montigny 1989), and patients suffering from anxiety disorders seem to be more sensitive to CCK treatment (Bradwejn et al. 1991, 1992; de Leeuw et al. 1996), suggesting a regulatory role for the peptide in these disorders (Hebb et al. 2005 ; Singh et al. 1991).

Accordingly, the CCK and the opioid system can antagonistically affect pain and emotion. Moreover, they overlap anatomically (e.g., in anterior cingulate cortex (ACC) and periaqueductal gray; Beinfeld et al. 1981), suggesting a functional relation. While it has been shown that both systems directly regulate pain processing, it has not yet been demonstrated if they, in a similar way, can modulate the emotional valence of other external stimuli. We hypothesize that the regulatory role of these systems can be generalized to an overall emotional regulation (including how we perceive the external world) invoked by prefrontal cognitive and motivational goals. In the present study, we investigated if pharmacological treatment with CCK and opioids could modulate the valence of visual stimuli using the international affective picture system (IAPS; Lang 1999; Lang et al. 1999) displaying either unpleasant or neutral content. The induced emotional state was manipulated with the CCK_b-receptor agonist pentagastrin and the mu-opioid receptor agonist remifentanil. We predicted that pentagastrin would increase the perception of unpleasantness in the pictures, whereas remifentanil would decrease the unpleasantness in the pictures.

Materials and methods

Subjects

A double-blind, placebo-controlled, repeated measurement design was conducted in 13 healthy male volunteers. The included subjects were right-handed, non-smokers, 20–34 years of age (mean=25 years, SD=4) with no present or past history of substance dependence or psychiatric illness. Experimentally induced emotions were achieved by exposure to affective pictures and pharmacologically manipulated with two drugs and placebo. Self-ratings, psychological tests, and physiological parameters were recorded. All experimental procedures were approved by the regional ethical committee in Stockholm.

Design

Twelve sets of neutral and twelve sets of unpleasant pictures, each containing seven pictures, were selected from the emotional standardized photographic material IAPS (Lang 1999). Pictures were chosen as to balance the sets for arousal and emotional valence. This was based on the published data for a relevant population (adult male subjects) as given in the instruction manual and affective ratings (Lang et al. 1999). The reference population used scales ranging from 1–9, where higher number indicated higher intensity of arousal and positive valance. Applied reference values were based on a study made by Bradley et al. (2001). Data on the selected images are given in Table 1.

Picture selection

Based on a study made by Bradley et al. (2001), we defined neutral pictures as all pictures with a valance value of 4.30

Table 1 Reference values for picture selection and picture set design

	Valance	Arousal
Selection of pictures		
Neutral pictures	4.30–5.90	1.55–3.75
Neutral pictures displaying faces	4.12–6.06	1.55–5.04
Unpleasant pictures	<4	>5
Unpleasant pictures displaying non-mutilated faces	<3.5	>5
Picture sets (average range)		
Neutral picture sets	4.93–5.26	2.51–3.25
Unpleasant picture sets	2.28–2.81	5.53–6.38

Pictures used in the experiment were taken from the emotional standardized photographic material IAPS (Lang 1999; Lang et al. 1999). The scales range from 1–9, where higher number indicates higher intensity of arousal and positive valance. Each picture set contained seven pictures and were balanced for facial and non-facial content. The presented values represent the average of the pictures valance and arousal

to 5.90 and an arousal value of 1.55 to 3.75 (Table 1). We used a more lenient inclusion criterion for pictures containing faces to increase the total amount of face stimuli and balance the blocks (valance value of 4.12 to 6.06 and arousal values ranging from 1.55 to 5.04). Every neutral block contained seven pictures including three images displaying face stimuli and four pictures displaying a non-facial motive that were randomly assigned from each category. The unpleasant pictures could be divided into four different categories depending on their motive: mutilated faces, mutilated human body parts, unpleasant motives displaying a face, or an unpleasant motive with a non-facial content. The valance and arousal threshold for the three first categories was <4 and >5, respectively; corresponding values for the last category were <3.5 and >5. Every unpleasant block of pictures contained seven pictures (randomly assigned from each category) including four face stimuli (two mutilated and two non-mutilated), one with mutilated body parts without any shown face and three with a non-facial content. A few of the IAPS pictures were considered as dated or not carrying relevant emotional information in the Swedish culture and were therefore excluded.

Picture set composition

We randomly assigned pictures to the 24 sets (12 neutral and 12 unpleasant blocks). The neutral blocks displayed an average value of 4.93–5.26 (range) in valance and 2.51–3.25 in arousal (Table 1). The six blocks with an average arousal value closest to 5.00 were included in the experiment, and the remaining blocks were included in the recognition test as unfamiliar pictures. Every unpleasant block displayed an average of 2.28–2.81 in valance and an average of 5.53–6.38 in arousal. The six blocks with the lowest valance value were included in the experiment and the other six in the recognition test.

Time line

Information pertaining to the experiment was given both as oral and written instructions to the subjects. Screening questionnaires for state/trait, anxiety level, and depression were given before the experiment. The subjects were presented to twelve consecutive picture blocks with every other displaying a neutral or an unpleasant content (Fig. 1). Before each presentation, the participants were injected intravenously with one of three possible drugs: (1) pentagastrin (0.1 μg/kg) (Pentagastrin®, John Bell Croyden, England), (2) remifentanil (0.0625 μg/kg) (Ultiva®, Glaxo Smith Kline), or (3) saline (placebo). During the experiment, heart rate was sampled every 10 s (Ohmeda, Biox 3740 pulsoximeter, model 15). After each presentation block self-ratings of the subjects' emotional experiences were performed with visual analogue scales (VAS) and the State-Trait Anxiety Inventory—State (Spielberger et al. 1970). Additionally, oral descriptions of subjective experiences were written down. When all the twelve blocks had been presented, a surprise recognition test was conducted 20 min after the last picture presentation.

Experimental procedures

The screening included the following queries: general information, Edinburgh Handedness Inventory, the Swedish Universities Scales of Personality (Gustavsson et al. 2000),

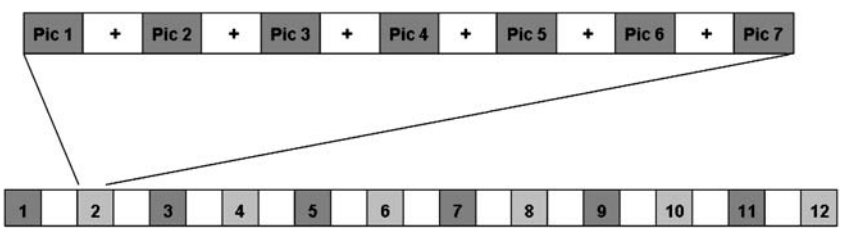


Fig. 1 The experimental setup. The *bottom row* displays 12 picture blocks, six neutral (*dark grey*) and six unpleasant (*light grey*); between each block is a 10-min pause (*white boxes*). *Top row*: one block contains seven pictures (*grey boxes*), between each picture is a pause (+) varying from 4 to 6 s

Montgomery–Asberg depression scale (Montgomery and Asberg 1979), State-Trait Anxiety Inventory (STAI; Spielberger et al. 1970), and Anxiety State Index (Reiss et al. 1986). These tests were used to screen subjects before inclusion, and in a latter stage serve as data correlating individual data with behavioral observations.

Each drug treatment occurred four times during the experiment and was administered as an open procedure with unknown syringe content both for the subject and the doctor injecting the drug (double-blind design). The procedure of administering the drugs was performed in a highly organized manner to keep the double blindness. Before every picture trial, three injections were given. The first syringe was given during 40 s and could contain either remifentanil or saline; the second syringe was given quickly (5 s) and could contain either pentagastrin or saline, and the third syringe always contained saline and was given during 10 s. After the injections were performed, approximately 30 s passed before the picture presentation started. Remifentanil was given during a longer time to avoid adverse effects that can easily be provoked by a quicker administration. In addition, remifentanil reaches its peak blood concentration after approximately 60 s (Michelsen and Hug 1996) and has an approximate half time of 3 min (Beers and Camporesi 2004), i.e., there was a significant effect during the whole picture presentation. Previous studies with pentagastrin have shown a peak autonomic response after 50 s (Radu et al. 2003). Importantly, the symptoms decline very quickly for pentagastrin and usually disappear after 4 min (Radu 2005). Conclusively, the idea was to catch the maximum effect of the drugs during the picture trials. However, these peak and half-times are only approximate and vary highly inter-individually.

We chose to use a dose of 0.1 μg/kg pentagastrin to induce reliable emotional responses but avoid inducing panic attacks (the lowest panicogenic dose of pentagastrin described to be psychotropic is 0.11 μg/kg (Abelson and Liberzon 1999), and a dose of 0.05 μg/kg can induce both a significant increase of autonomic responses and experienced discomfort (Radu et al. 2003)). The same logic was applied for remifentanil treatment. We performed a pilot study in which we chose a remifentanil dose that did not induce strong unspecific drug effects of drowsiness and nausea, but still had an effect on emotional perception.

The pictures presented with the drugs were either of neutral or unpleasant content giving rise to a 3×2 (drug × picture) block design with six possible experimental conditions: (1) pentagastrin treatment with neutral pictures (PN), (2) pentagastrin treatment with unpleasant pictures (PU), (3) remifentanil treatment with neutral pictures (RN), (4) remifentanil treatment with unpleasant pictures (RU), (5) saline (placebo) treatment with neutral pictures (SN), and (6) saline treatment with unpleasant pictures (SU). The order of treatments was randomized in two main blocks, with the reservation that two drug treatments of the same kind could not be consecutive as to avoid pharmacological adaptation. The block randomizations occurred in a similar way; a neutral block was always followed by an unpleasant and vice versa. Furthermore, all participants were shown the same blocks but in an individualized random order. The pictures were displayed on a 1×1-m screen 1.5 m in front of the subject. The picture blocks duration was approximately 70 s, and between every block presentation was a 10-min pause. Each picture was displayed for 5 s, between every picture was a pause that was either 4, 5, or 6 s so the subjects could not expect when the stimulus would be presented. The order of pictures and pauses were randomized in advanced in each picture set and did not vary between the subjects. During the picture presentations, the subjects were instructed to concentrate on the center of the screen. Before the presentations and during the pauses between the pictures, a hair-cross was displayed. Subjects were instructed to fixate on the cross in between the pictures and keep that fixation during the picture presentation.

Subjective experiences of the pictures and the drug effects were rated after each presentation with six 100-mm VAS (ranging from "minimum" to "maximum"). The scales rated the: (1) unpleasantness of the pictures' contents, (2) unpleasantness of the drug, (3) pleasantness of the pictures' contents, (4) pleasantness of the drug, (5) concentration (mental focus) on the pictures, and (6) drowsiness. We specifically emphasized to the subjects that they should separate how they perceived the drug itself and how the perceived the pictures. Upon questioning after the experiment, all subjects indicated that they had maintained a separation of these two ratings.

The recognition test was performed 20 min after the last picture presentation and included all 84 pictures presented in the experiment and 84 unfamiliar pictures from the block design. Each picture was displayed for 3 s, and between every picture was a 2-s pause. As soon as the picture was shown, the subjects judged as quickly as possible if the picture had occurred in the experiment or not by pressing a button. Participants were asked to emphasize accuracy, not speed. A total number of 168 pictures were shown consecutively. Reaction time and errors were of interest, linking the two parameters to the pictures' experimental condition.

Statistical analysis

The statistic analysis of the VAS ratings and the score in the recognition test was carried out using non-parametric tests. Friedman's test was used to calculate the main effect of picture content and drug effect, while the Wilcoxon signed rank test evaluated the specific contrasts. The correlation

Table 2 The self-ratings for concentration (mental focus) and drowsiness for each experimental condition

Concentration	SN	PN	RN	SU	PU	RU
Average	80.35	68.81	75.31	85.58	84.31	78.31
SD	18.02	18.75	20.40	12.90	12.24	14.85
Drowsiness	SN	PN	RN	SU	PU	RU
Average	5.23	9.62	22.73	3.62	6.65	22.65
SD	3.90	10.56	19.12	3.00	8.67	14.24

SN Saline neutral pictures, *PN* pentagastrin neutral pictures, *RN* remifentanil neutral pictures, *SU* saline unpleasant pictures, *PU* pentagastrin unpleasant pictures, *RU* remifentanil unpleasant pictures

analysis examining the relationship between the STAI and the VAS ratings was carried out using the non-parametric test Spearman's rho. A parametric two-way repeated measurement analysis of variance analyzed the main effects of drug treatment and picture content on heart rate and reaction time. Specific contrasts were then evaluated with the Student's *t* test. A value of $P<0.05$ was considered as significant. All the results from the specific contrasts (both parametric and non-parametric) were corrected for multiple comparisons using the Bonferroni correction.

Results

Background data

Subjects reported slightly higher levels of concentration when exposed to unpleasant pictures than neutral pictures ($F=58.5$, $P<0.001$), but no difference was found between drugs (Table 2). They also reported low levels of drowsiness (mean VAS=11.75, SD=8.70). Subjective ratings for drowsiness were significantly different for both drugs ($F=27.8$, $P<0.001$) and picture types ($F=48.6$, $P<0.01$). The subjects reported less drowsiness for unpleasant pictures, but more drowsiness with remifentanil irrespectively of picture content [(neutral pictures) $W=44.5$, $P<0.001$; (unpleasant pictures) $W=39.0$, $P<0.001$]. Pentagastrin, on the other hand, did not significantly affect drowsiness in comparison to saline (Table 2).

We observed no effect from the drugs ($F=1.55$, n.s.) on memory performance in the recognition test. However, the picture content showed a small but yet significant effect on memory in that the unpleasant images were slightly better remembered than neutral images ($F=43.6$, $P<0.01$; Fig. 2) with no differences in reaction time (picture type: $F=1.50$, n.s., drug type: $F=1.88$, n.s.).

Effects of the drugs on how the pictures were perceived

Ratings of how unpleasant the pictures were perceived

As expected, the ratings of the experienced unpleasantness for the different picture types (unpleasant/neutral content) were significantly higher for the unpleasant images than for neutral images ($F=68.1$, $P<0.001$; Fig. 3a). Furthermore, there was a main effect for drug type on the experience of how unpleasant the pictures were perceived ($F=14.2$, $P<0.001$). After pentagastrin injection, the subjects rated the pictures as more unpleasant, both in the case of neutral images (Wilcoxon signed rank test, $W=24.5$, $P<0.01$) as

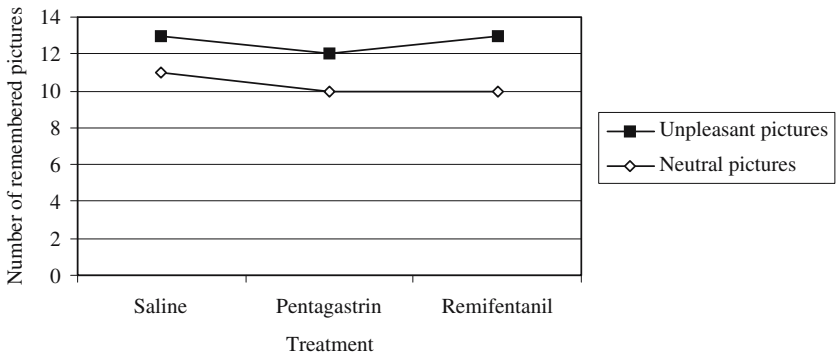


Fig. 2 Effect of drug treatment on memory. The unpleasant pictures were slightly better remembered than neutral ones in the recognition test ($P<0.01$). There were no significant differences between the drug treatments. Saline neutral pictures (*SN*): mean=11.00, SD=2.42; pentagastrin neutral pictures (*PN*): mean=10.23, SD=2.28; remifentanil neutral pictures (*RN*): mean=10.31, SD=2.63; saline unpleasant pictures (*SU*): mean=12.54, SD=1.33; pentagastrin unpleasant pictures (*PU*): mean=12.38, SD=1.04; remifentanil unpleasant pictures (*RU*); mean=12.85, SD=1.41

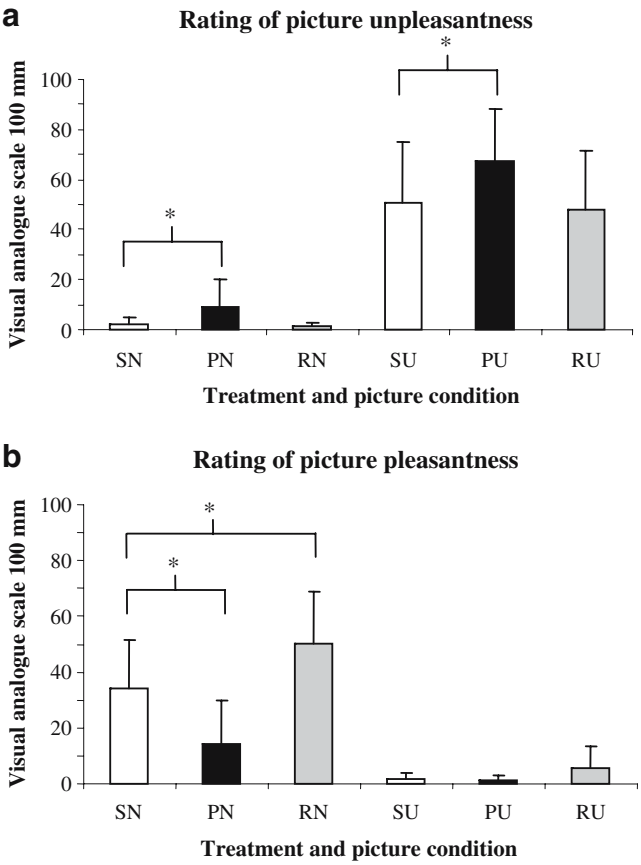


Fig. 3 Effect of the drugs on picture ratings. **a** After pentagastrin treatment, pictures were rated as more unpleasant than after saline treatment irrespectively of neutral or unpleasant pictures ($P<0.01$). No differences were found between saline and remifentanil treatment. Saline neutral pictures (*SN*): mean=2.15, SD=2.42; pentagastrin neutral pictures (*PN*): mean=8.88, SD=11.10; remifentanil neutral pictures (*PN*): mean=1.27, SD=1.52; saline unpleasant pictures (*SU*): mean=50.54, SD=24.32; pentagastrin unpleasant pictures (*PU*): mean=67.42, SD=20.84; remifentanil unpleasant pictures (RU): mean=47.62, SD=23.69. **b** Neutral picture were rated as more pleasant after remifentanil treatment in the neutral condition compared to saline treatment ($P<0.01$). No differences were seen in the unpleasant picture conditions. Saline neutral pictures (*SN*): mean=34.08, SD=17.56; pentagastrin neutral pictures (*PN*): mean=14.46, SD=15.24; remifentanil neutral pictures (*RN*): mean=50.27, SD=18.76; saline unpleasant pictures (*SU*): mean=1.58, SD=2.17; pentagastrin unpleasant pictures (*PU*): mean=1.35, SD=1.61; remifentanil unpleasant pictures (*RU*): mean=5.46, SD=8.10

well as when unpleasant images were presented ($W=41$, $P<0.01$; Fig. 3a). There were no significant differences in ratings of unpleasantness between remifentanil and saline.

Ratings of how pleasant the pictures were perceived

There was an overall significance of the two main factors drug and picture type [(drug) $F=15.7$, $P<0.001$; (picture type) $F=67.1$, $P<0.001$] on rated pleasantness of the picture content (Fig. 3b). While neutral pictures were rated as more pleasant after remifentanil treatment as compared with saline treatment ($W=36.5$, $P<0.01$), no difference was seen for the unpleasant pictures ($W=10.5$, n.s.). After pentagastrin administration, lower ratings of pleasantness in the picture content were reported for neutral pictures compared to saline treatment ($W=40.5$, $P<0.01$). No effects were noted for the unpleasant images ($W=1.5$, n.s.).

Ratings of how the drugs were perceived

Ratings of how unpleasant the drug was perceived

When the subjects rated the experienced unpleasantness of the injected drug, there was also an overall effect of drug

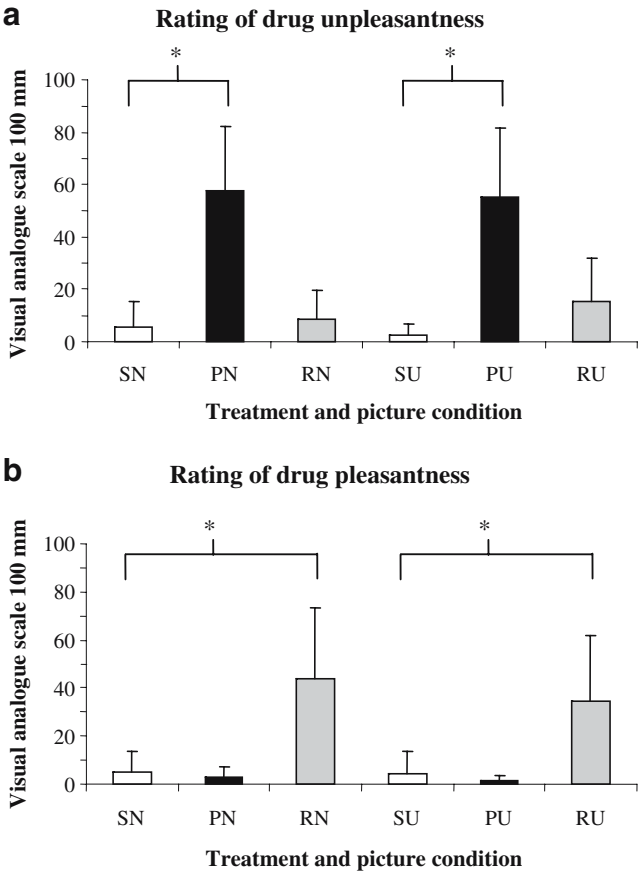


Fig. 4 Effect of the drugs on emotional state. **a** Pentagastrin was perceived as more unpleasant than saline in both picture conditions ($P<0.001$). Saline neutral pictures (*SN*): mean=5.69, SD=9.72; pentagastrin neutral pictures (*PN*): mean=57.81, SD=24.30; remifentanil neutral pictures (*RN*): mean=8.42, SD=11.38; saline unpleasant pictures (*SU*): mean=2.58, SD=4.22; pentagastrin unpleasant pictures (*PU*): mean=55.23, SD=26.55; remifentanil unpleasant pictures (*RU*): mean=15.08, SD=16.79. **b** Remifentanil was perceived as more pleasant compared to saline no matter picture content ($P<0.001$). Saline neutral pictures (*SN*): mean=4.88, SD=8.78; pentagastrin neutral pictures (*PN*): mean=2.81, SD=4.74; remifentanil neutral pictures (*RN*): mean=44.08, SD=29.02; saline unpleasant pictures (*SU*): mean=4.19, SD=9.45; pentagastrin unpleasant pictures (*PU*): mean=1.62, SD=1.91; remifentanil unpleasant pictures (*RU*): mean=34.42, SD=27.55

(F=46.6, P<0.001). Pentagastrin induced unpleasantness to the same extent irrespective of the picture content (W=45.5, P<0.001 in both cases; Fig. 4a).

Ratings of how pleasant the drug was perceived

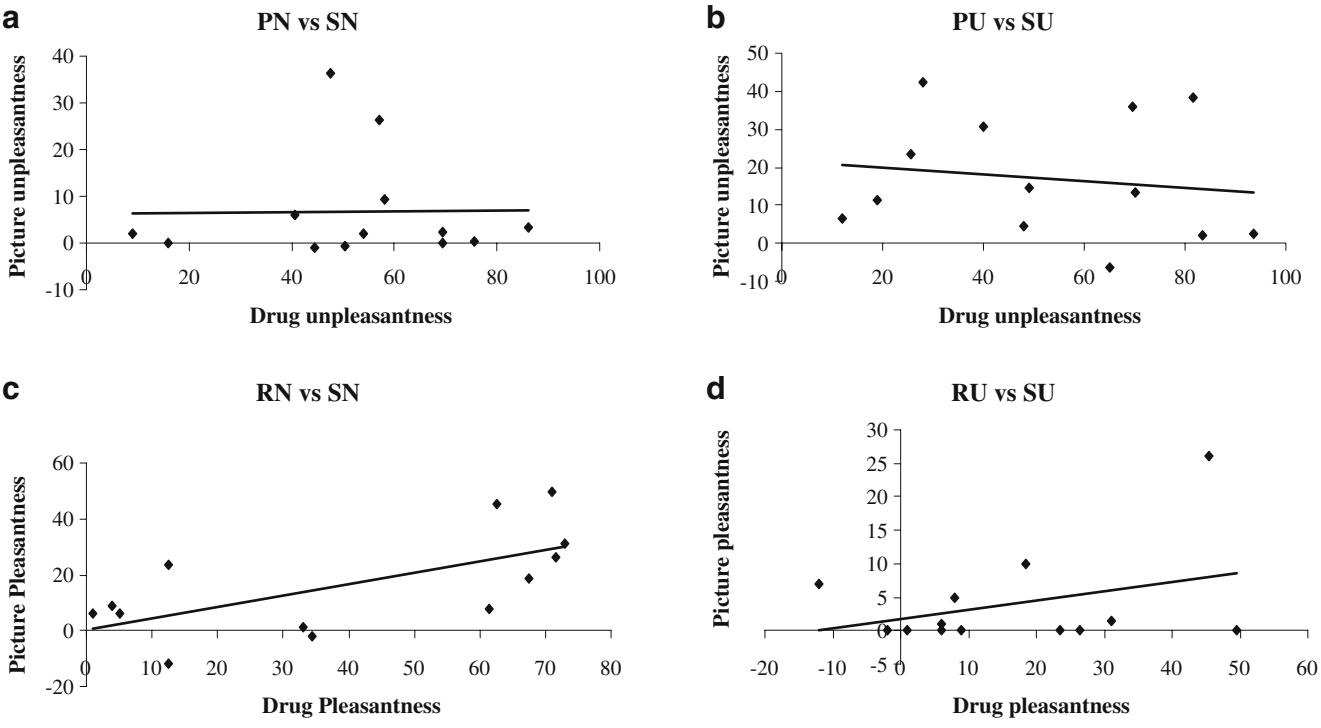
When subjects were probed for the experienced pleasantness of the drug, there was a main effect of drug treatment (F=42.9, P<0.001). Remifentanil was experienced as more pleasant irrespective of picture content [(neutral images) W=60, P<0.001; (unpleasant images) W=50.5, P<0.001] (Fig. 4b).

Relation between ratings of drug and ratings of pictures

There was no correlation between increase in unpleasantness ratings of the drug and increase in unpleasantness ratings of how the pictures were perceived for pentagastrin (P=0.14 for neutral pictures; P=0.48 for unpleasant pictures; Fig. 5a and b). However, we observed a significant correlation between increase in ratings of pleasantness of drug and ratings of pleasantness of neutral picture for remifentanil (P=0.022, r=0.63 for neutral pictures; P=0.022, r=0.63 for unpleasant pictures; Fig. 5c and d).

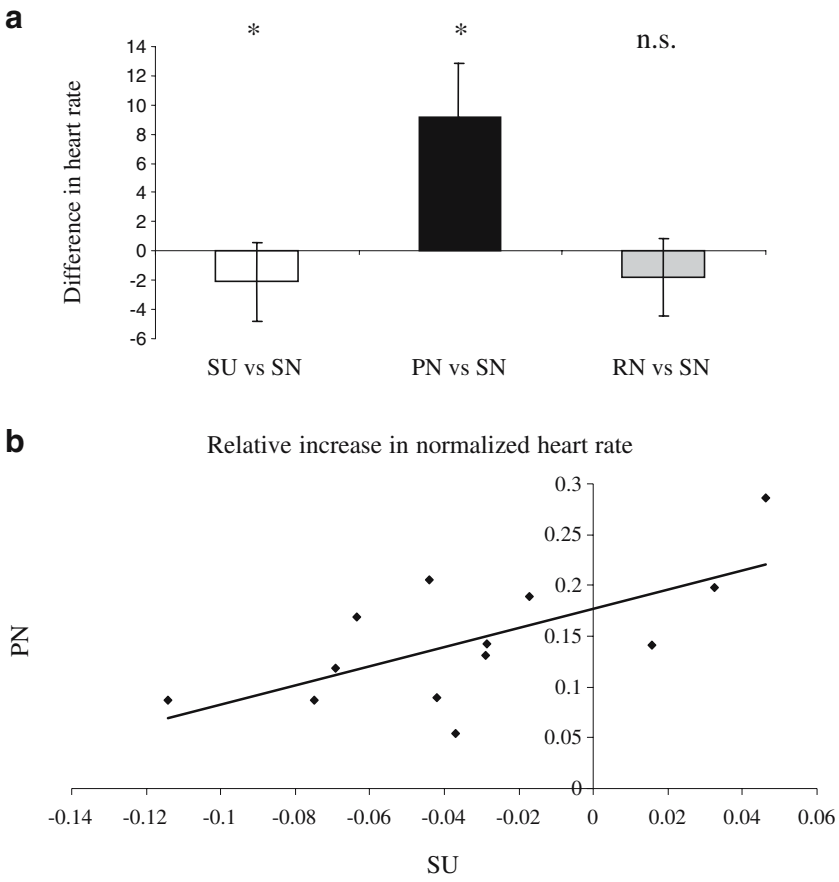
Effects on heart rate

There was a significant effect of drug treatment on heart rate (F=62.08, p<0.001). We also performed three post hoc tests to analyze how treatment or unpleasantness affected the heart rate. We observed that unpleasant pictures significantly decreased the heart rate compared with neutral pictures (heart rate in SU vs SN; t=−2.80, p<0.05), while pentagastrin increased heart rate compared with saline treatment (heart rate in PN vs SN; t=8.90, P<0.001; Fig. 6a). There was a tendency for a decrease in heart rate for remifentanil (heart rate in RN vs SN, t=−2.44), which did not reach significance after Bonferroni correction. To study whether there was a relation between the changes in heart rate



PN = Pentagastrin neutral pictures
SN = Saline neutral pictures
PU = Pentagastrin unpleasant pictures
SU = Saline unpleasant pictures
RN = Remifentanil neutral pictures
RU = Remifentanil unpleasant pictures

Fig. 5 Correlation between how the drug and the pictures were perceived. No correlation was observed between how unpleasant pentagastrin was experienced and how unpleasant the pictures were rated (**a** and **b**). In contrast, a significant correlation was observed between how pleasant remifentanil was experienced and how pleasant the neutral (**c**; P=0.022, r=0.63) and the unpleasant pictures (**d**; P=0.022, r=0.63) were rated. All ratings were made on a visual analogue scale from 0 to 100 mm



SU = Saline unpleasant pictures
SN = Saline neutral pictures
PN = Pentagastrin neutral pictures
RN = Remifentanil neutral pictures

Fig. 6 Effects on heart rate. **a** There was a significant heart rate decrease in the saline unpleasant (*SU*) picture condition compared to the saline neutral (*SN*) picture condition ($t=-2.80$, $p<0.05$). A significant heart rate increase was observed in the pentagastrin neutral (*PN*) picture condition vs the saline neutral (*SN*) picture condition ($t=8.90$, $P<0.001$). A trend for a decrease in heart rate was observed when subjects were treated with remifentanil. **b** The normalized heart rate response for each subject in the PN condition correlated with the normalized heart rate response in the SU condition ($P<0.05$, $r=0.67$; the responses in the different conditions is expressed as the relative change in relation to the saline neutral picture condition)

due to pentagastrin and unpleasant pictures, we normalized the average heart rate responses for PN and SU with the heart rate response in SN (i.e., the responses in the different conditions is expressed as the relative change in relation to the SN condition). We were able to show a positive correlation between the normalized heart rate after pentagastrin with the normalized heart rate after saline ($P<0.05$, $r=0.67$; Fig. 6b). Thus, subjects who showed the lowest decrease in heart rate for unpleasant pictures after saline administration showed the highest increase in heart rate after pentagastrin treatment when presented to neutral pictures.

STAI-T

Here, we tested whether there was a relation between general anxiety level and how unpleasant pictures were experienced in general and after pentagastrin treatment. We observed a significant negative correlation between STAI-T scores and pentagastrin-induced unpleasantness ratings of the pictures [in PU vs SU: $P<0.001$ (two-tailed), $r=-0.83$; Fig. 7a]. Thus, the subjects with the highest STAI-T scores (the higher score the more anxious) were least effected by pentagastrin in how they experienced unpleasant pictures. We also observed a weak tendency of a positive correlation between STAI-T scores and pentagastrin-induced drug unpleasantness (in PN vs SN: $P=0.14$, $r=0.32$; Fig. 7b).

Discussion

In the present study, we show that subjects perceive both neutral and unpleasant pictures as more unpleasant after administration of the CCK agonist pentagastrin, while neutral pictures are experienced as more pleasant after treatment with the mu-opioid agonist remifentanil. To our knowledge, this is the first study that systematically shows that external input other than noxious signals can be modulated by the opioid and CCK system. We suggest that these neuromodulatory systems are important in regulating emotional processes in a similar way as they modulate pain processing.

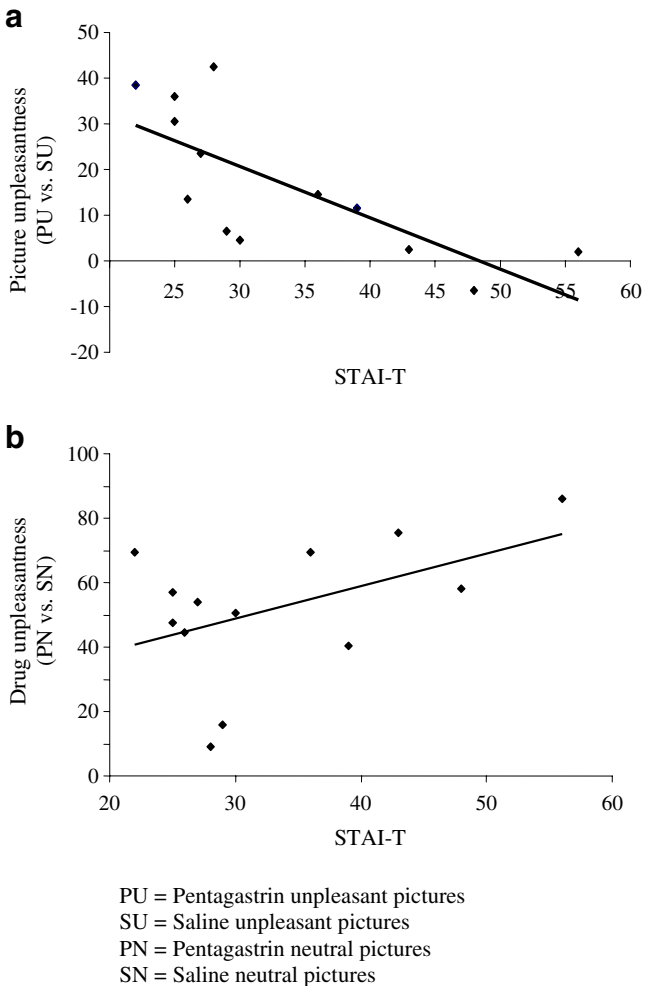


Fig. 7 Relation between anxiety levels and pentagastrin's effects on picture and drug rating. **a** STAI-T scores correlated negatively with pentagastrin induced unpleasantness of pictures rating scores (pentagastrin unpleasant pictures vs saline unpleasant pictures; $P<0.001$, $r=-0.83$). **b** There was no statistical significant correlation between how unpleasant pentagastrin was experienced and STAI-T although a week positive trend was observed

Although there is no direct evidence that CCK_b agonists cross the blood brain barrier (BBB), several studies suggest that these drugs act directly on the central nervous system. It has been shown that intravenous CCK-4 administration changes hippocampal activity, although the neuronal input from the peripheral CCK activation was cut off (Dahl 1987). Moreover, CCK-8 that has a 10,000-fold higher affinity to peripheral CCK_b receptors but does not cross the BBB, can induce similar but more intense gastrointestinal side effects (including nausea), but in contrast to CCK-4, it does not induce panic attacks or anxiety (de Montigny 1989). It is therefore hard to conceive that the anxiety responses provoked by CCK-4 or pentagastrin (Benkelfat et al. 1995; Bradwejn et al. 1991; de Montigny 1989) treatments are solely mediated by peripheral mechanisms. Thus, our working hypothesis is that pentagastrin has the ability to pass the BBB and act upon central CCK receptors to interact with cognitive and emotional processes. Although unlikely, as for previous studies on CCK_b agonists and anxiety induction, we cannot exclude that the mechanisms are solely peripherally mediated.

Earlier studies have used CCK agonists as an experimental model for anxiety and panic (Bradwejn et al. 1991; Dauge and Lena 1998; de Leeuw et al. 1996; Radu et al. 2003) and focused on their effect on internal states. The CCK system may also change the processing of external noxious input in general (Fields and Basbaum 1999; Hebb et al. 2005) and in the placebo/nocebo response (Benedetti 1996; Colloca and Benedetti 2005; Levine et al. 1978; Petrovic et al. 2002). In the present behavioral study, we generalized this idea to include other external inputs such as visual stimuli. We hypothesized that complex visual stimuli, especially those with an emotional content, would be experienced as more unpleasant after treatment with pentagastrin, in analogy with its effect on pain processing. In line with our hypothesis, we found that both neutral and unpleasant pictures were experienced as more unpleasant after pentagastrin treatment (Fig. 3a). The drug also induced a higher discomfort in agreement to previous research (Bradwejn et al. 1991; Radu et al. 2002, 2003; Fig. 4a). Some of the pentagastrin effects we observed in the study might have been mediated via peripheral mechanisms, e.g., nausea which all of the subjects experienced to a small extent when given pentagastrin. Importantly, several subjects experienced nausea during the remifentanil trials as well, but they still rated the pictures as highly pleasant. Thus, although we cannot completely separate central from peripheral actions of pentagastrin, the present study suggest that nausea per se cannot explain why pictures are perceived as more unpleasant.

In analogy with the CCK system, the opioid system has both been studied in relation to its involvement in opioid analgesia (Fields and Basbaum 1999) and in emotional processing such as pleasure and reward experiences (Berridge 2003). To activate the opioid system, we used remifentanil that can easily penetrate the BBB (Beers and Camporesi 2004) and act upon central processing of pain and emotional experiences (Petrovic et al. 2002).

We suggest that the CCK and the opioid system work in an antagonistic fashion in modulating emotional processes. The results were, however, more complex for the remifentanil treatment than for the CCK treatment. Although there was a trend that the unpleasant pictures were experienced as more pleasant after remifentanil treatment, we failed to detect a difference in how unpleasant the aversive pictures were rated between the remifentanil and saline treatment (although we had hypothesized that opioid treatment would lower this rating). One interpretation of this result is that the mu-opioid system is not involved in suppressing emotional

aversive processing, as it suppresses nociceptive processing. This would be in line with animal studies which have shown that the delta, but not the mu-opioid, system is involved in the modulation of aversive non-noxious processing. For example, delta-deficient mice act more anxious and depressive, while mu-deficient knockout mice lack depressive behavior (Filliol et al. 2000; Kieffer and Gaveriaux-Ruff 2002). Remifentanil treatment increased ratings of pleasantness both for the neutral pictures and for the drug effect on mood (Figs. 3b and 4b). These findings indicate that a mu-opioid agonist may be more effective in augmenting a pleasant response than suppressing an unpleasant process to external input, which is in line with the idea that we perceive emotions in a multidimensional space and not via a mutually exclusive one-dimensional scale (Larsen et al. 2001; Rolls 1995; Schimmack 2001).

The ratings of mental focus indicated that there was no difference in how well the subjects could concentrate on the pictures between the treatments, although the subjects showed a slight increase in drowsiness after remifentanil treatment (Table 2). Although the unpleasant pictures were better remembered than the neutral (Fig. 2), a finding that previously has been shown (Richardson et al. 2004), there was no difference between the treatments in how well the pictures were remembered. These results indicate that the difference in focus and drowsiness between the treatments did not have a great impact on how well the subjects attended to and memorized the stimuli.

Although the tested drugs significantly modulate the emotional perception of pictures, we cannot completely separate whether this is caused by a change in mood or because the two neuroregulatory systems have specific modulation on emotional processing of visual input. However, available research suggest that there is an interaction between emotion and visual processing, e.g., the activity in fusiform face area is augmented when fearful faces are shown (compared with neutral faces) or when unpleasant pictures are shown (compared with neutral pictures), an effect probably induced by the amygdala (Vuilleumier and Pourtois 2007). We have hypothesized that this emotionally induced effect on visual processing is a key component in our results. Thus, although the pictures may have induced a more negative emotion, the core visual processing may also have changed. The subjects also rated how they perceived the pictures and not what emotions they perceived after viewing the pictures. However, there is no perfect division between what is a "visually induced negative emotion" or an experience of a more unpleasant picture, and finer experiments including imaging studies have to be performed to understand the separation between the two processes.

On a related topic, it cannot be excluded that the subjects were confused between ratings of change in mood induced by the drugs and ratings of how they perceived the pictures after treatment. We asked the subjects to be aware of this difference and not confuse the two experiences. In the post-viewing interviews, the subjects indicated that they had no difficulty in separating the rating of how the drug affected their emotional state and how they perceived the pictures. Importantly, there was no correlation between pentagastrin-induced general unpleasantness perception and the change in how unpleasant pictures were rated after pentagastrin treatment, indicating no relation between the change in internal state and experience of external input (Fig. 5a and b). For remifentanil, we observed a positive correlation between drug-induced change in mood and how the treatment changed external input (Fig. 5c and d), i.e., the more pleasure the subjects experienced in general, the more pleasurable did they rate the external input. Possibly, studies

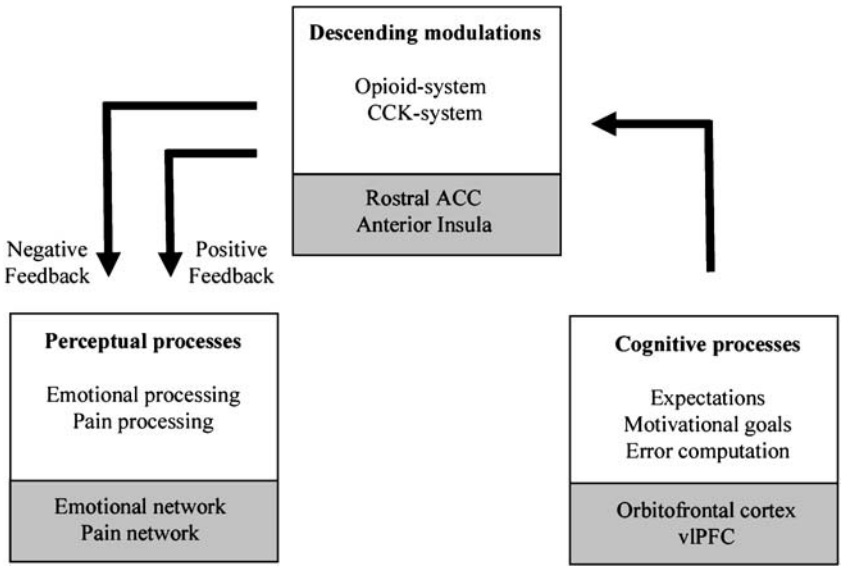


Fig. 8 A model for top-down control of emotions. A suggested model of how the CCK and the opioid projections may be a part of a descending neuromodulatory system used in top-down control of pain and emotion. In this model, cognitive processes such as expectations and motivation in the orbitofrontal and ventrolateral prefrontal cortex (*vlPFC*) drive attentional modulation which can use the opioid and the CCK projections (in anterior cingulate cortex (ACC) and anterior insula) to both suppress or augment emotional and pain processes

using CCK and opioid blockers in a similar context may be more effective in studying these issues, as they do not induce large changes in mood.

It has been shown that the opioid and the CCK system are involved in mediating the placebo and the nocebo response (Benedetti 1996; Colloca and Benedetti 2005; Levine et al. 1978; Petrovic et al. 2002). As both conditions are dependant on expectation and social interaction, one could speculate that the CCK and the opioid system may be driven by higher cognitive functions. In fact, these neuromodulatory systems could be used to modulate specific processes in the brain such as emotion and pain, leaving other processes unaffected. This idea is supported by functional–anatomical data which show that both opioid receptors (Petrovic et al. 2005; Vogt et al. 1993) and CCK receptors (Beinfeld et al. 1981) are found in large concentrations in the ACC. The ACC is also involved in attentional mechanisms (Bush et al. 2000), and placebo studies have shown an overlapping activation for opioids and the placebo response in the ACC (Petrovic et al. 2002). Thus, ACC may be viewed as a region where attention and different neuromodulatory systems interact (Petrovic et al. 2002). Furthermore, ACC has extensive projections to other regions, e.g., amygdala, prefrontal cortex, and insula (Pandya et al. 1981), which are also involved in emotional processing. Imaging studies (Benkelfat et al. 1995; Schunck et al. 2006) have shown that CCK administration activates ACC and insula, in line with the suggestion that these areas could be involved in emotional regulation. Although the present study cannot answer the question whether cognitive processes interact with the opioid and the CCK system, the ability of these systems to modulate emotional processing as well as pain and their close association with networks involved in attentional processes suggest that they may be used in top-down regulation of pain and emotion (Fig. 8).

In line with previous studies, heart rate decreased for unpleasant pictures (Bradley et al. 2001) but increased after pentagastrin treatment (Radu et al. 2003). Heart rate decrease for viewing unpleasant material has been suggested to mirror a passive fear state (Lang et al. 2000). This state, often referred to as post-encounter phase, is associated with a minimal degree of movement and a heart rate decrease after detection of a threat to avoid a confrontation (Fanselow 1994; Lang et al. 2000). Similarly, the heart rate increase after pentagastrin treatment is in line with the involvement of the CCK system in an active fear state closely linked to panic attacks (Bradwejn and Koszycki 2001). Active fear states, also called circa-strike phase, may be induced when there is an imminent or ongoing attack by a threat (Fanselow 1994). In our data, the subjects with the most expressed heart rate increase for pentagastrin had the least expressed mitigation in heart rate for unpleasant pictures (Fig. 6). One interpretation of this finding is that subjects who are more prone to react with an active coping strategy (related to circa-strike phase) when treated with pentagastrin will suppress passive coping strategies (related to the post-encounter phase) when viewing unpleasant pictures. This would be in line with the suggestion that passive fear mechanisms and active fear mechanisms are mutually inhibiting each other (Fanselow 1994). We also showed that those subjects being most prone to anxiety in general (scoring high on the STAI-T questionnaire) showed the least change in how unpleasant pictures were perceived after pentagastrin treatment (Fig. 7a), although they showed a positive trend correlation for pentagastrin-induced drug unpleasantness (Fig. 7b). Upon inspection, we noted that four of the five subjects with a STAI-T >35 had the highest unpleasantness ratings on unpleasant pictures after placebo treatment. Thus, the finding above (shown in Fig. 7a) may represent a ceiling effect. These findings clearly need further investigation, but imply that there are different fear states in humans in which there is a balance between internal mood state vs experience of external stimuli as well as passive vs active coping strategies. How these findings translate to clinical populations is unclear, although it is well known that anxiety and panic attacks have components of both active and passive coping strategies (McNaughton and Corr 2004; Lang et al. 2000).

Taken together, the results suggest that external stimuli other than noxious may be modulated by the same specific descending systems that are involved in pain regulation, thus, suggesting a more general function for these neuromodulatory systems. We propose that the opioid system and the CCK system are involved in different types of top-down regulation of external input including both nociceptive and visual stimuli. We know from earlier research that CCK is involved in anxiety disorders including panic attacks (Singh et al. 1991), but its regulatory role on emotional processing is more obscure. From a clinical point of view, our results could lead to a better understanding of how affective disorders might be able to manipulate our perception of the external world.

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References

Abelson JL, Liberzon I (1999) Dose response of adrenocorticotropin and cortisol to the CCK-B agonist pentagastrin. Neuropsychopharmacology 21:485–494

Beinfeld MC, Meyer DK, Eskay RL, Jensen RT, Brownstein MJ (1981) The distribution of cholecystokinin immunoreactivity in the central nervous system of the rat as determined by radioimmunoassay. Brain Res 212:51–57

Beers R, Camporesi E (2004) Remifentanil update: clinical science and utility. CNS Drugs 18:1085–1104

Benedetti F (1996) The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. Pain 64:535–543

Benedetti F, Amanzio M, Maggi G (1995) Potentiation of placebo analgesia by proglumide. Lancet 346:1231

Benedetti F, Amanzio M, Maggi G, Vighetti S, Asteggiano G (2006) The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. J. Neurosci 26:12014–12022

Benkelfat C, Bradwejn J, Meyer E, Ellenbogen M, Milot S, Gjedde A et al (1995) Functional neuroanatomy of CCK4-induced anxiety in normal healthy volunteers. Am J Psychiatry 152:1180–1184

Berridge KC (2003) Pleasures of the brain. Brain Cogn 52:106–128

Bradley MM, Codispoti MC, Bruce N, Lang PJ (2001) Emotion and motivation I: Defensive and appetitive reactions in picture processing. Emotion 1:276–298

Bradwejn J, Koszycki D (2001) Cholecystokinin and panic disorder: past and future clinical research strategies. Scand J Clin Lab Invest Suppl 234:19–27

Bradwejn J, Koszycki D, Shriqui C (1991) Enhanced sensitivity to cholecystokinin tetrapeptide in panic disorder. Clinical and behavioral findings. Arch Gen Psychiatry 48:603–610

Bradwejn J, Koszycki D, Annable L, Couetoux du Tertre A, Reines S, Karkanias C (1992) A dose-ranging study of the behavioral and cardiovascular effects of CCK-tetrapeptide in panic disorder. Biol Psychiatry 32:903–912

Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4:215–222

Cesselin F (1995) Opioid and anti-opioid peptides. Fundam Clin Pharmacol 9:409–933

Colloca L, Benedetti F (2005) Placebo and painkillers: is mind really a matter? Nat Rev Neurosci 6:545–552

Dahl D (1987) Systemically administered cholecystokinin affects an evoked potential in the hippocampal dentate gyrus. Neuropeptides 10:165–173

Dauge V, Lena I (1998) CCK in anxiety and cognitive processes. Neurosci Biobehav Rev 22:815–825

de Leeuw AS, Den Boer JA, Slaap BR, Westenberg HG (1996) Pentagastrin has panic-inducing properties in obsessive compulsive disorder. Psychopharmacology 126:339–344

de Montigny C (1989) Cholecystokinin tetrapeptide induces panic-like attacks in healthy volunteers. Preliminary findings. Arch Gen Psychiatry 46:511–517

Fanselow MS (1994) Neural organization of the defensive behaviour system responsible for fear. Psychon Bull Rev 1:429–439

Fields HL, Basbaum AI (1999) Central nervous system mechanisms of pain modulation. In: Wall PD, Melzack R (eds) Textbook of pain, 4th edn. Churchill Livingstone, London, pp 309–329

Filliol D, Ghozland S, Chluba J, Martin M, Matthes HW, Simonin F et al (2000) Mice deficient for delta- and mu-opioid receptors exhibit opposing alterations of emotional responses. Nat Genet 25:195–200

Frith C, Dolan RJ (1997) Brain mechanisms associated with top-down processes in perception. Philos Trans R Soc B Biol Sci 352:1221–1230

Gustavsson J, Bergman H, Edman G, Ekselius L, von Knorring L, Linder J (2000) Swedish Universities Scales of Personality (SSP): construction, internal consistency and normative data. Acta Psychiatr Scand 102:217–225

Hebb AL, Poulin JF, Roach SP, Zacharko RM, Drolet G (2005) Cholecystokinin and endogenous opioid peptides: interactive influence on pain, cognition, and emotion. Prog Neuropsychopharmacol Biol Psychiatry 29:1225–1238

Hodes RL, Howland EW, Lightfoot N, Cleeland CS (1990) The effects of distraction on responses to cold pressor pain. Pain 41:109–114

Kieffer BL, Gaveriaux-Ruff C (2002) Exploring the opioid system by gene knockout. Prog Neurobiol 66:285–306

Koob GF, Stinus L, Le Moal M, Bloom FE (1989) Opponent process theory of motivation: neurobiological evidence from studies of opiate dependence. Neurosci Biobehav Rev 13:135–140

Lang PJ (1999) The international affective picture system: digitized photographs. Center of the study of emotion and attention [CSEA-NIMH]. The Center for Research in Psychophysiology, University of Florida, Gainesville, FL

Lang PJ, Bradley MM, Cuthbert BN (1999) The international affective picture system (IAPS): instruction manual and affective ratings. Technical report A-5. The Center for Research in Psychophysiology, University of Florida, Gainesville, FL

Lang PJ, Davis M, Ohman, A (2000) Fear and anxiety: animal models and human cognitive psychophysiology. J Affect Disord 61: 137–159

Larsen JT, McGraw AP, Cacioppo JT (2001) Can people feel happy and sad at the same time? J Pers Soc Psychol 81:684–696

Levine JD, Gordon NC, Fields HL (1978) The mechanism of placebo analgesia. Lancet 312:654–657

McNaughton N, Corr PJ (2004) A two-dimensional neuropsychology of defense: fear/anxiety and defensive distance. Neurosci Biobehav 28:285–305

Melzack R, Casey KL (1968) Sensory, motivational and central control determinants of pain: a new conceptual model. In: Kenshalo D (ed) The skin senses. Thomas Springfield, IL, pp 423–443

Mesulam MM (1998) From sensation to cognition. Brain 121: 1013–1052

Michelsen LG, Hug CC Jr (1996) The pharmacokinetics of remifentanil. J Clin Anesth 8:679–682

Mobbs D, Weiskopf N, Lau HC, Featherstone E, Dolan RJ, Frith CD (2006) The Kuleshov effect: the influence of contextual framing on emotional attributions. Soc Cogn Affect Neurosci 1:95–106

Montgomery SA, Asberg M (1979) A new depression scale designed to be sensitive to change. Br J Psychiatry 134:382–389

Ochsner KN, Gross JJ (2005) The cognitive control of emotion. Trends Cogn Sci 9:242–249

Pandya DN, Van Hoesen GW, Mesulam MM (1981) Efferent connections of the cingulate gyrus in the rhesus monkey. Exp Brain Res 42:319–330

Petrovic P, Petersson KM, Ghatan PH, Stone-Elander S, Ingvar M (2000) Pain-related cerebral activation is altered by a distracting cognitive task. Pain 85:19–30

Petrovic P, Kalso E, Petersson KM, Ingvar M (2002) Placebo and opioid analgesia—imaging a shared neuronal network. Science 295:1737–1740

Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, Ingvar M (2005) Placebo in emotional processing—induced expectations of anxiety relief activate a generalized modulatory network. Neuron 46:957–969

Radu D (2005) Aspects on the psychopharmacology of cholecystokinin. Thesis, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm

Radu D, Ahlin A, Svanborg P, Lindefors N (2002) Anxiogenic effects of the CCK(B) agonist pentagastrin in humans and dose-dependent increase in plasma C-peptide levels. Psychopharmacology 161:396–403

Radu D, Ahlin A, Svanborg P, Lindefors N (2003) Pentagastrin test for anxiety—psychophysiology and personality. Psychopharmacology 166:139–145

Reiss S, Peterson RA, Gursky DM, McNally RJ (1986) Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. Behav Res Ther 24:1–8

Richardson MP, Strange BA, Dolan RJ (2004) Encoding of emotional memories depends on amygdala and hippocampus and their interactions. Nat Neurosci 7:278–285

Rolls E (1995) A theory of emotion and consciousness, and its application to understandning the neural basis of emotion. In: Gazzaniga MS (ed) The cognitive neurosciences. Bradford, Cambridge, MA

Sadock JB, Sadock VA (2003) Kaplan and Sadock's synopsis of psychiatry behavioural sciences/clinical psychiatry, 9th edition edn. Lippincott Williams and Wilkins, Philadelphia, USA

Schimmack U (2001) Pleasure, displeasure, and mixed feelings: are semantic opposites mutually exclusive? Cognition and Emotion 15:81–97

Schunck T, Erb G, Mathis A, Gilles C, Namer IJ, Hode Y et al (2006) Functional magnetic resonance imaging characterization of CCK-4-induced panic attack and subsequent anticipatory anxiety. Neuroimage 31:1197–1208

Singh L, Lewis AS, Field MJ, Hughes J, Woodruff GN (1991) Evidence for an involvement of the brain cholecystokinin B receptor in anxiety. Proc Natl Acad Sci U S A 88:1130–1133

Spielberger CD, Gorsuch RL, Lushene RE (1970) Manual for the State-Trait Anxiety Inventory (self evaluation questionnaire). Consulting Psychologists Press, Palo Alto, CA

Sullivan MJ, Rodgers WM, Kirsch I (2001) Catastrophizing, depression and expectancies for pain and emotional distress. Pain 91:147–154

Turner JA, Jensen MP, Romano JM (2000) Do beliefs, coping, and catastrophizing independently predict functioning in patients with chronic pain? Pain 85:115–125

Weisenberg M (1998) Cognitive aspects of pain and pain control. Int J Clin Exp Hypn 46:44–61

Vogt BA, Sikes RW, Vogt LJ (1993) Anteroir cingulated cortex and the medial pain system. In: Vogt BA, Gabriell M (eds) Neurobiology of cingulated cortex and limbic thalamus: a comprehensive handbook. Birkhäuser, Boston. pp 313–340

Vuilleumier P, Pourtois G. (2007) Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. Neuropsychologia 7:174–194