

REVIEW

WHEN WORDS ARE PAINFUL: UNRAVELING THE MECHANISMS OF THE NOCEBO EFFECT

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Abstract—The nocebo effect is a phenomenon that is opposite to the placebo effect, whereby expectation of a negative outcome may lead to the worsening of a symptom. Thus far, its study has been limited by ethical constraints, particularly in patients, as a nocebo procedure is per se stressful and anxiogenic. It basically consists in delivering verbal suggestions of negative outcomes so that the subject expects clinical worsening. Although some natural nocebo situations do exist, such as the impact of negative diagnoses upon the patient and the patient's distrust in a therapy, the neurobiological mechanisms have been understood in the experimental setting under strictly controlled conditions. As for the placebo counterpart, the study of pain has been fruitful in recent years to understand both the neuroanatomical and the neurochemical bases of the nocebo effect. Recent experimental evidence indicates that negative verbal suggestions induce anticipatory anxiety about the impending pain increase, and this verbally-induced anxiety triggers the activation of cholecystokinin (CCK) which, in turn, facilitates pain transmission. CCK-antagonists have been found to block this anxiety-induced hyperalgesia, thus opening up the possibility of new therapeutic strategies whenever pain has an important anxiety component. Other conditions, such as Parkinson's disease, although less studied, have been found to be affected by nocebo suggestions as well. All these findings underscore the important role of cognition in the therapeutic outcome, and suggest that nocebo and nocebo-related effects might represent a point of vulnerability both in the course of a disease and in the response to a therapy. © 2007 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: placebo, cholecystokinin, endogenous opioids, anxiety, pain, Parkinson's disease.

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Abbreviations: ACC, anterior cingulate cortex; ACTH, adrenocorticotrophic hormone; CCK, cholecystokinin; HPA, hypothalamic–pituitary–adrenal; PFC, prefrontal cortex; PI, posterior insula; PO, parietal operculum.

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Top-down control of sensory input plays a fundamental role in shaping global perceptual experience. Whereas this is well recognized and studied in many sensory modalities, such as the visual, somatosensory and auditory systems (Frith and Dolan, 1997; Mesulam, 1998; Pessoa et al., 2003), new lines of experimental evidence suggest that this top-down cognitive and emotional modulation also occurs in the clinical setting, whereby the intensity and severity of symptoms can be shaped by the psychological state of the patient. Early studies showed that complex psychological factors can modulate both the patient's perception of pain and his/her response to an analgesic treatment. For example, it was shown that pretreating patients with placebos, i.e. inert substances that the patient believes to be effective, lowered the effectiveness of painkillers, while pretreatment with active painkillers enhanced the analgesic effect of placebos (Kantor et al., 1966; Laska and Sunshine, 1973). Likewise, it was found that verbal suggestions can change the direction of nitrous oxide's action from analgesia to hyperalgesia (Dworkin et al., 1983).

Most research of this kind has been pursued in the field of pain and analgesia, and the study of placebo and nocebo effects has been crucial to unravel the neurobiological mechanisms of this top-down modulation. Since many reviews have been written on the placebo effect in the past few years (Benedetti et al., 2005; Colloca and Benedetti, 2005; Hoffman et al., 2005; Pacheco-Lopez et al., 2006), the present review describes only what we know today about the mechanisms of the nocebo effect, a phenomenon whereby anticipation and expectation of a negative outcome may induce the worsening of a symptom. As these effects occur in the clinical setting, they have important implications for both therapy and patient–provider interaction.

PLACEBO AND NOCEBO EFFECTS

The placebo effect has been studied extensively from both a psychological and biological perspective, but in recent times placebo research has focused on the neural mechanisms, both from the neurochemical and the neuroanatomical viewpoint. Placebos are known to powerfully affect

the brain in different pathological conditions, like pain, motor disorders and depression, and in different systems and apparatuses, such as the immune and endocrine system (Benedetti et al., 2005; Colloca and Benedetti, 2005; Hoffman et al., 2005; Pacheco-Lopez et al., 2006). It has been shown that this may occur through both expectation and conditioning mechanisms, but expectation of the therapeutic benefit seems to play a crucial role, at least in pain, Parkinson's disease and depression (Benedetti et al., 2003b; Finniss and Benedetti, 2005; Hoffman et al., 2005), whereas immune and hormonal placebo responses are likely to involve conditioning mechanisms (Benedetti et al., 2003b; Pacheco-Lopez et al., 2006).

Recently, placebo-induced expectations have been analyzed with sophisticated neurobiological tools that have uncovered specific mechanisms at both the biochemical, anatomical and cellular level. In fact, expectations have been found to activate endogenous opioids (Levine et al., 1978; Grevert et al., 1983; Benedetti, 1996; Amanzio and Benedetti, 1999; Benedetti et al., 1999; Zubieta et al., 2005) and pain modulating networks (Petrovic et al., 2002), to decrease the transmission in pain pathways (Wager et al., 2004; Price et al., 2006), to induce a release of dopamine in the striatum (de la Fuente-Fernandez et al., 2001), and to affect the activity of single neurons in the subthalamic nucleus (Benedetti et al., 2004). There is also some experimental evidence that different serotonin-related brain regions are involved in the placebo response in depression (Leuchter et al., 2002; Mayberg et al., 2002; Benedetti et al., 2005).

Overall, the search for the neurobiological mechanisms of the placebo effect has given us information about the intricate interaction that exists between a complex mental activity, such as expectation and anticipation of clinical benefit, and different neuronal systems which are capable of modifying the course of a symptom and/or a disease. It has also given us important information about new ways of running clinical trials (Colloca and Benedetti, 2005; Finniss and Benedetti, 2005).

On the other hand, mainly due to ethical constraints, much less is known about the nocebo counterpart. In fact, whereas the induction of placebo responses is certainly ethical in many circumstances (Benedetti and Colloca, 2004; Colloca et al., 2004), the induction of nocebo responses represents a stressful and anxiogenic procedure, because verbally-induced negative expectations of symptom worsening may lead to a real worsening. Of course, a nocebo procedure is unethical in patients, but some recent studies in healthy volunteers and some others in animals have shed new light on this phenomenon.

The term nocebo ("I shall harm") was introduced in contraposition to the term placebo ("I shall please") by some authors to distinguish the pleasing from the noxious effects of placebo (Kennedy, 1961; Kissel and Barrucand, 1964; Hahn, 1985, 1997). If the positive psychosocial context (i.e. the verbal context), which is typical of the placebo effect, is reversed in the opposite direction, the nocebo effect can be studied.

It is important to point out that the study of the nocebo effect is the study of the negative psychosocial context around the patient and the treatment, and its neurobiological investigation is the analysis of the effects of this negative context on the patient's brain and body. As for the placebo effect, the nocebo effect, or response, follows the administration of an inert substance (the nocebo, or negative placebo) along with the suggestion that the subject will get worse. However, the term nocebo-related effect will also be used throughout this review to indicate symptom worsening following negative expectations but without the administration of any inert substance.

IMAGING THE BRAIN WHEN EXPECTING NEGATIVE OUTCOMES

Modern brain imaging techniques have been fundamental in the understanding of the neurobiology of negative expectations. It should be noted that no inert substance is given in these studies, and the experimenter typically uses verbal suggestions. Therefore, in this case it would be better to talk about nocebo-related effects. Typically, the experimenter tells the subject about the forthcoming pain so as to make the subject expect a painful stimulation, and both the anticipatory phase and the post-stimulus phase are analyzed. Most of this research has been carried out in the field of pain.

By using this experimental approach, it has been shown that the perceived intensity of a painful stimulus following negative expectation of pain increase is higher than in the absence of negative expectations. For example, Sawamoto et al. (2000) found that expectation of painful stimulation amplifies perceived unpleasantness of innocuous thermal stimulation. These psychophysical findings were correlated to enhanced transient brain responses to the nonpainful thermal stimulus in the anterior cingulate cortex (ACC), the parietal operculum (PO) and posterior insula (PI). This enhancement consisted in both a higher intensity signal change (in ACC) and a larger volume of activated voxels (in PO and PI). Therefore, expecting a painful stimulus enhances both the subjective unpleasant experience of an innocuous stimulus and the objective responses in some brain regions.

Overall, negative expectations may result in the amplification of pain (Koyama et al., 1998; Price 2000; Dannecker et al., 2003), and several brain regions, like ACC, the prefrontal cortex (PFC), and the insula, have been found to be activated during the anticipation of pain (Chua et al., 1999; Hsieh et al., 1999; Ploghaus et al., 1999; Porro et al., 2002, 2003; Koyama et al., 2005; Lorenz et al., 2005; Keltner et al., 2006). These effects are in the opposite direction of those elicited by positive expectations, whereby expectation of reduced pain is investigated. In fact, in some studies in which both positive and negative outcomes have been studied with the same experimental approach, the modulation of both subjective experience and brain activation has been found. For example, in the study by Koyama et al.

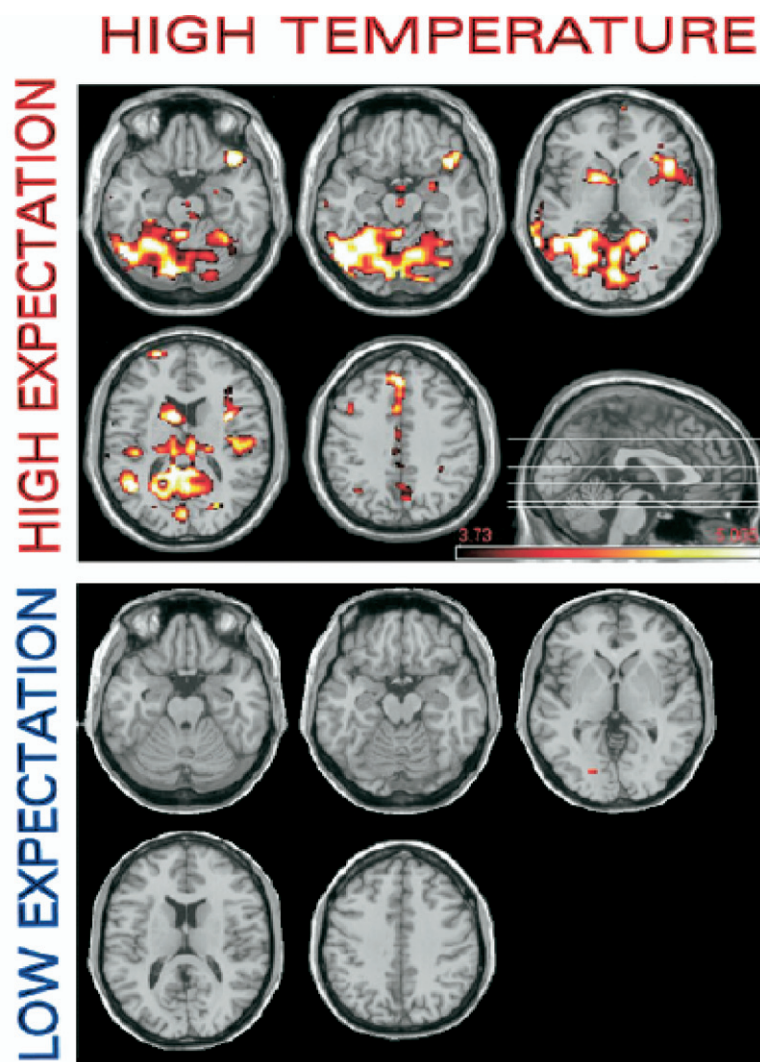


Fig. 1. Brain fMRI responses to a high-temperature stimulus when the subject expects a high (above) or a low (below) intensity stimulation. Note that expectation of a high-intensity noxious stimulus activates different brain regions, such as the thalamus, insular cortex, somatosensory cortex, ACC as well as the orbitofrontal cortex, amygdala, ventral striatum, and the nucleus cuneiformis in the brainstem. By contrast, expectation of a low-intensity noxious stimulus induces less fMRI activation (from Keltner et al., 2006).

(2005), as the magnitude of expected pain increased, activation increased in the thalamus, insula, PFC, and ACC. By contrast, expectations of decreased pain reduced activation of pain-related brain regions, like the primary somatosensory cortex, the insular cortex and ACC. In a different electroencephalogram (EEG) study in which source localization analysis was performed, Lorenz et al. (2005) found a modulation of the electrical dipole in the secondary somatosensory cortex by nocebo-like and placebo-like suggestions. The dipole was modulated in the same direction of expectations, shrinking when pain decrease was expected and expanding when pain increase was anticipated.

More recently, Keltner et al. (2006) found that the level of expected pain intensity alters perceived pain intensity along with the activation of different brain regions. By using two visual cues, each conditioned to one of two noxious thermal stimuli (high and low), Keltner et al. (2006) showed

that subjects reported higher pain when the noxious stimulus was preceded by the high-intensity visual cue. By comparing the brain activations produced by the two visual cues, these authors found significant differences in the ipsilateral caudal ACC, the head of the caudate, cerebellum, and the contralateral nucleus cuneiformis (nCF) (Fig. 1). Interestingly, the imaging results of this study indicate that expectation and noxious stimulus intensity act in an additive manner on afferent pathways activated by cutaneous noxious thermal stimulation.

By taking all these imaging studies together, it appears clear that expectation of either low or high painful stimuli has a strong influence on the perceived pain. As noted above, although these studies deal with negative expectations, neither placebos nor nocebos (inert substances) were administered, thus these effects can be better called nocebo-related effects, in which only verbal suggestions were given.

NOCEBO HYPERALGESIA AND ITS BIOCHEMISTRY

Like placebo analgesia, nocebo hyperalgesia has represented the best model to study the mechanism of the nocebo effect. To obtain placebo analgesia, a placebo (inert treatment) is given along with verbal suggestions of improvement. Likewise, to obtain nocebo hyperalgesia, an inert treatment is given along with verbal suggestions of worsening.

A modulation of pain perception by placebo and nocebo that is dependent on expectation has been shown by Benedetti et al. (2003b). In this study, in one group of subjects a pharmacological pre-conditioning with ketorolac, a nonopioid analgesic, was performed for 2 days in a row and then ketorolac was replaced with a placebo on the third day along with verbal suggestions of analgesia. This procedure induced a strong placebo analgesic response. In order to see whether this placebo response was due to the pharmacological pre-conditioning, in a second group of subjects the same pre-conditioning procedure with ketorolac was carried out but the placebo was given on the third day along with verbal suggestions that the drug was a hyperalgesic agent. These verbal instructions were enough not only to block placebo analgesia completely, but also to produce hyperalgesia. These findings clearly show that nocebo hyperalgesia depends on expectation of pain increase, even though a pre-conditioning analgesic procedure is done.

In 1997, Benedetti et al. (1997) ran a trial in postoperative patients with proglumide, a nonspecific cholecystokinin (CCK) antagonist for both CCK-A and CCK-B receptors, or CCK-1 and CCK-2 according to the new classification (Noble et al., 1999). The situation was a post-surgical manipulation that induces expectations of pain increase, so that the patients were given an inert treatment that they expected to be painful. In that study, proglumide was found to prevent nocebo hyperalgesia in a dose-dependent manner, even though it is not a specific painkiller, thus suggesting that this effect is mediated by CCK. In fact, a dose as low as 0.05 mg was totally ineffective whereas a dose increase to 0.5 and 5 mg proved to be effective. As CCK is also involved in anxiety mechanisms, Benedetti et al. (1997) and Benedetti and Amanzio (1997) hypothesized that proglumide affected anticipatory anxiety of the impending pain. Importantly, this effect was not antagonized by naloxone, thus indicating that it is not opioid-mediated. However, due to ethical constraints in these patients, these effects were not investigated further.

In order to overcome the ethical limitations that are inherent to any clinical study, a similar experimental approach was used in healthy volunteers. In fact, Benedetti et al. (2006), by studying experimental ischemic arm pain in volunteers, performed a detailed neuropharmacological study of nocebo hyperalgesia. It was found that the oral administration of an inert substance, along with verbal suggestions of hyperalgesia, induced hyperalgesia and hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, as assessed by means of adrenocorticotrophic hor-

mone (ACTH) and cortisol plasma concentrations. Both nocebo-induced hyperalgesia and HPA hyperactivity were blocked by diazepam, one of the most used anti-anxiety benzodiazepines, which suggests that anxiety plays a major role in these effects. By contrast, the administration of the mixed CCK type-A/B receptor antagonist, proglumide, blocked nocebo hyperalgesia completely, but had no effect on HPA hyperactivity, thus suggesting a specific involvement of CCK in the hyperalgesic but not in the anxiety component of the nocebo effect. Most important, diazepam and proglumide did not show analgesic properties on baseline pain, as they acted only on the nocebo-induced pain increase. Therefore, these data indicate a close relationship between anxiety and nocebo hyperalgesia, but they also indicate that proglumide does not act by blocking anticipatory anxiety of the impending pain, as previously hypothesized by Benedetti et al. (1997) and by (Benedetti and Amanzio 1997), but rather it interrupts a CCKergic link between anxiety and pain. In other words, these data suggest that CCK turns anxiety into pain and that CCK-antagonists may prevent this effect (Fig. 2).

A support to this view comes from animal studies, in which CCK antagonists have been found to prevent anxiety-induced hyperalgesia. In particular, in a social-defeat model of anxiety in rats, it has recently been shown that CI-988, a selective CCK-B receptor antagonist, prevented anxiety-induced hyperalgesia, with an effect that was similar to that produced by the established anxiolytic chlordiazepoxide (Andre et al., 2005). Similarly, other studies that used selective CCK-A and CCK-B receptor antagonists in animals and humans have shown the important role of CCKergic systems in the modulation of anxiety and in the link between anxiety and hyperalgesia (Hebb et al., 2005).

THE ROLE OF CCK IN PAIN, COGNITION AND EMOTION

Besides the understanding of the mechanisms of the nocebo effect, these studies on nocebo hyperalgesia have been useful to understand the role of CCK in both pain and some complex functions, such as cognition and emotion. In fact, in recent years CCK has been found to play a crucial role in many complex physiological and psychological functions (Hebb et al., 2005). For example, there has been accumulating evidence that CCK acts as a neuromodulator of pain and anxiety, although the exact mechanisms are still unclear (Vanderhaeghen et al., 1975; Beinfeld, 1983; Baber et al., 1989; Crawley and Corwin, 1994; Hebb et al., 2005). CCK is found in the brain as an octapeptide (CCK-8) and its distribution in the brain matches that of the opioid peptides at both the spinal and supraspinal level (Stengaard-Pedersen and Larsson, 1981; Gall et al., 1987; Gibbins et al., 1987; Benedetti, 1997), suggesting a close interaction between the two neuropeptides.

Thus far, the involvement of CCK in nocebo hyperalgesia is based only on the pharmacological action of the CCK-antagonist proglumide (Benedetti et al., 1997, 2006). It should be noted that, although proglumide is a nonspecific CCK-A/B receptor antagonist with a weak preference

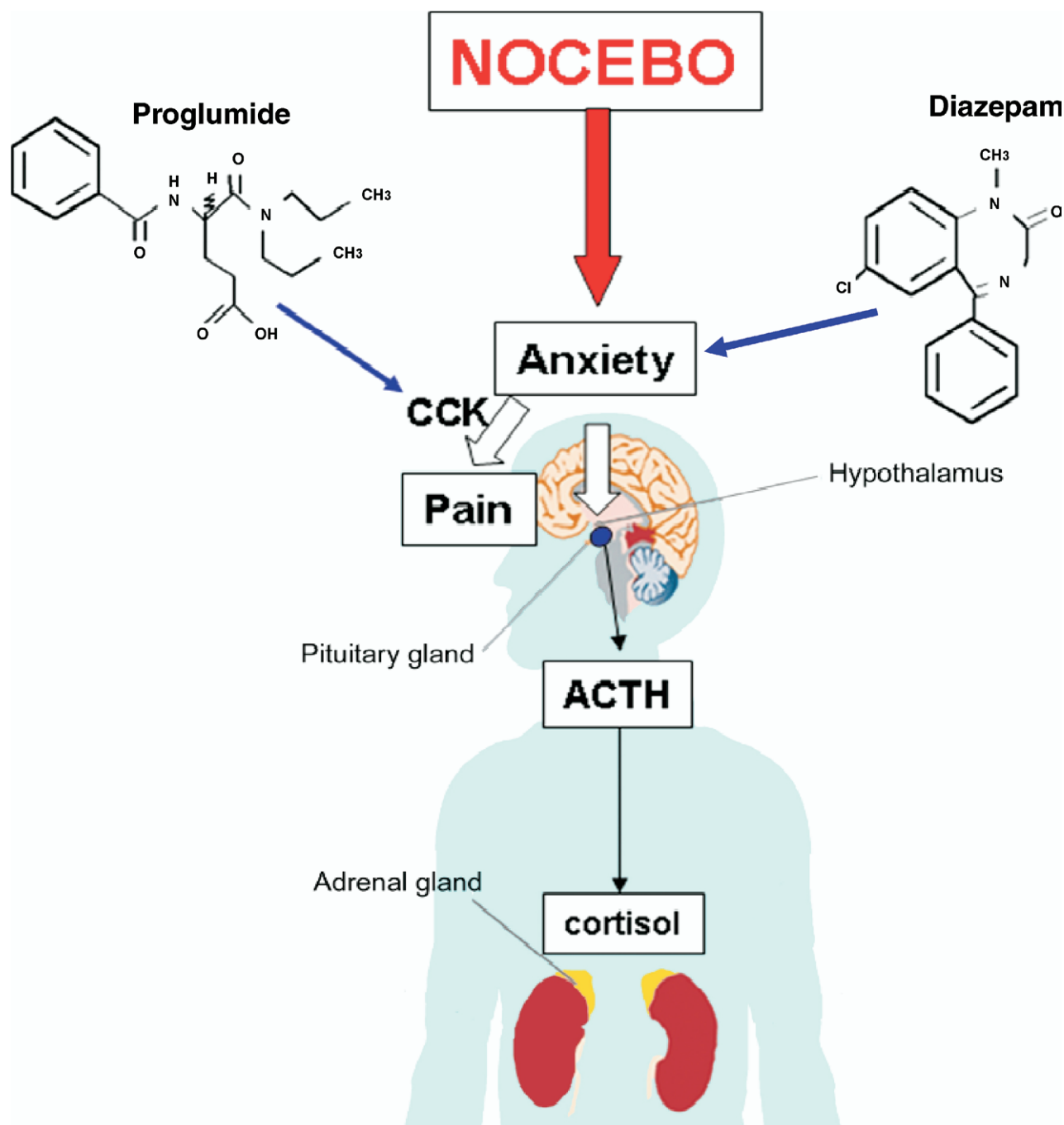


Fig. 2. Nocebo suggestions induce anxiety which, in turn, activates two different and independent biochemical pathways: a CCKergic facilitation of pain and the activation of the HPA axis, as assessed by means of plasma ACTH and cortisol increase. Whereas the anti-anxiety drug, diazepam, blocks anxiety, thus preventing both hyperalgesia and HPA hyperactivity, the CCK-antagonist, proglumide, acts on the CCKergic pathway only, thus inhibiting hyperalgesia but not HPA hyperactivity.

for CCK-A receptors (Benedetti, 1997), its action in the brain has been widely demonstrated in different conditions. There is behavioral and electrophysiological evidence that CCK is blocked by proglumide in the brain (Chiodo and Bunney, 1983; Suberg et al., 1985; Watkins et al., 1985a,b). The results obtained in humans on opioid potentiation by proglumide (Price et al., 1985; Lavigne et al., 1989; Benedetti et al., 1995; Benedetti, 1996) are in keep-

ing with the potentiation of morphine analgesia by the CCK-A antagonist devazepide in the rat (Dourish et al., 1988) and with the results obtained in animal studies using several CCK-B antagonists (Wiesenfeld-Hallin et al., 1990; Maldonado et al., 1993; Noble et al., 1993; Valverde et al., 1994; Xu et al., 1994; Andre et al., 2005). Proglumide has also been reported to block the anxiogenic effects of the tetrapeptide CCK-4 and caerulein, a CCK-8 agonist, indi-

cating an anti-CCK action in the CNS at the level of affective mechanisms (Harro et al., 1990; Harro and Vasar, 1991; van Meegen et al., 1994).

The antagonist action of CCK on endogenous opioids (Benedetti, 1997) is particularly interesting in light of the opposing effects of placebos and nocebos. In fact, today there is general agreement that placebo analgesia is mediated by endogenous opioids, specifically the mu-opioid receptors (Zubieta et al., 2005), at least in some circumstances (Benedetti et al., 2005; Colloca and Benedetti, 2005). Therefore, the findings on the involvement of CCK in nocebo hyperalgesia suggest that the opioidergic and the CCKergic systems may be activated by opposite expectations of either analgesia or hyperalgesia, respectively. In other words, as shown in Fig. 3, verbal suggestions of a positive outcome (pain decrease) activate endogenous mu-opioid neurotransmission, while suggestions of a negative outcome (pain increase) activate CCK-A and/or CCK-B receptors. This neurochemical view of the placebo–nocebo phenomenon, in which two opposite systems are activated by opposite expectations about pain, is in keeping with the opposite action of opioids and CCK in other studies (Benedetti, 1997; Hebb et al., 2005).

The involvement of CCK in both pain modulation and anxiety is particularly relevant to the nocebo effect. It is worth noting that some CCK-B receptor antagonists, like L-365,260, have a benzodiazepine-based chemical structure that is similar to the anxiolytic drug diazepam, which suggests a similarity of action of CCK-antagonists and

anti-anxiety drugs. However, it should be stressed that the study by Benedetti et al. (2006) suggests that nocebo suggestions activate two different and independent biochemical pathways, one blocked by proglumide and the other by diazepam (Fig. 2).

On the basis of all these considerations and the involvement of CCKergic systems in pain and anxiety mechanisms, nocebo hyperalgesia represents an interesting model to better understand when and how the endogenous pro-nociceptive systems are activated. In the case of CCK, besides the studies described above, the pro-nociceptive and anti-opioid action of this neuropeptide has been documented more recently in the brainstem. For example, it has been shown that CCK is capable of reversing opioid analgesia by acting at the level of the rostral ventromedial medulla, a region that plays a key role in pain modulation (Mitchell et al., 1998; Heinricher et al., 2001). It has also been shown that CCK activates pain facilitating neurons within the rostral ventromedial medulla (Heinricher and Neubert, 2004). The similarity of the pain facilitating action of CCK on brainstem neurons on the one hand and on nocebo mechanisms on the other hand, can stimulate and guide further research into the neurochemical mechanisms underlying nocebo-induced and/or anxiety-induced hyperalgesia.

It is also worth noting that CCK has been found to play a role in placebo analgesia. In fact, the CCK-antagonist proglumide has been found to potentiate placebo-induced analgesia, an effect that is probably due to the blockade of

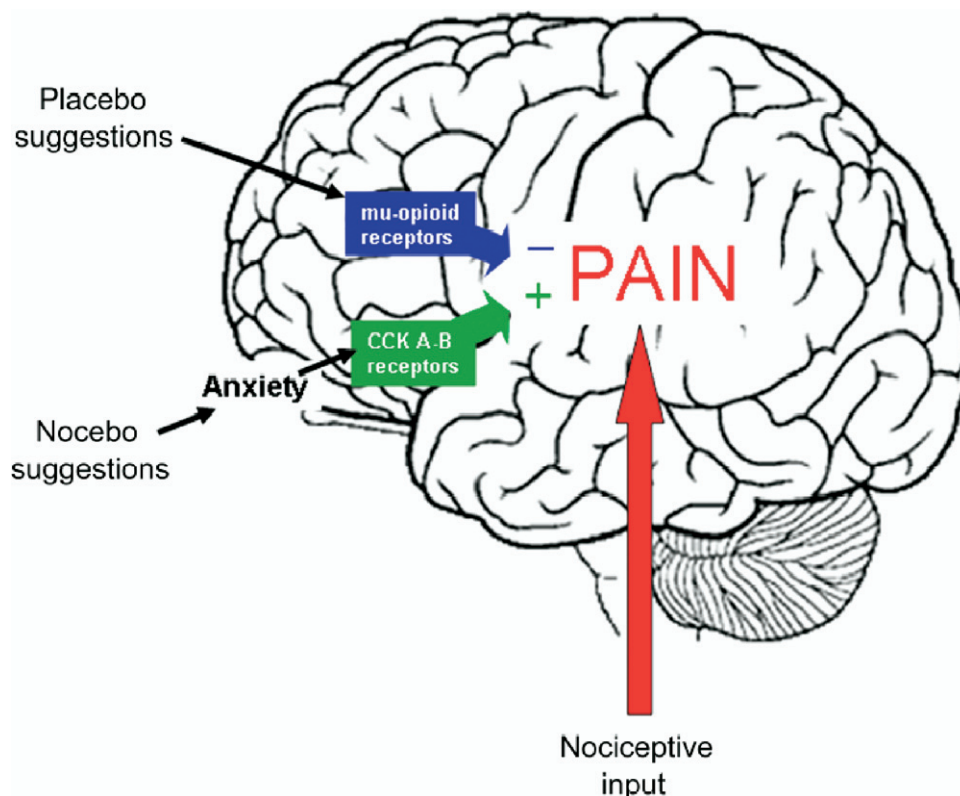


Fig. 3. Placebo and nocebo modulation of pain. Whereas placebo suggestions activate mu-opioid neurotransmission which inhibits pain, nocebo suggestions induce anxiety which activates CCK-A and/or CCK-B receptors that, in turn, enhance pain.

the anti-opioid action of CCK (Benedetti et al., 1995; Benedetti, 1996). Therefore, CCK appears to play a pivotal role in the psychological modulation of pain, antagonizing placebo-induced opioid release on the one hand and mediating nocebo-induced facilitation of pain on the other hand.

THE NOCEBO EFFECT IN PARKINSON'S DISEASE

Whereas nocebo hyperalgesia and, more in general, negative expectations of pain increase have been studied from both a behavioral, neuroanatomical and biochemical point of view, the neural mechanisms of the nocebo effect in conditions other than pain are poorly understood. Recently, Parkinson's disease, a disorder of movement characterized by tremor, muscle rigidity and bradykinesia (movements slow down), has represented an interesting model to investigate both the placebo and the nocebo effect. However, whereas in the first case some neurobiological mechanisms have been uncovered, such as dopamine release in the striatum (de la Fuente-Fernandez et al., 2001) and altered firing pattern in subthalamic nucleus neurons (Benedetti et al., 2004), in the second case only behavioral/clinical studies have been done.

In a study by Pollo et al. (2002), the velocity of movements was analyzed in Parkinson patients who had been implanted with electrodes in the subthalamic nuclei for deep brain stimulation, a highly effective anti-Parkinson treatment that is capable of relieving the motor parkinsonian symptoms. These patients were tested in two opposite conditions. In the first condition, they expected a good motor performance whereas in the second they expected a bad motor performance. It was found that these two opposite expectations modulate the therapeutic effect of the subthalamic nucleus stimulation. In fact, by analyzing the effect of subthalamic stimulation on the velocity of movement of the right hand with a movement analyzer, it was found the hand movement was faster when the patients expected a good motor performance than when they expected bad performance. Interestingly, all these effects occurred within minutes, which indicates that expectations induce neural changes very quickly.

In another study by Benedetti et al. (2003b), patients implanted for deep brain stimulation were tested for the velocity of movement of their right hand according to a double-blind experimental design in which neither the patient nor the experimenter knew whether the stimulator was turned off. The velocity of hand movement was assessed by means of a movement analyzer, characterized by a rectangular surface where the patients performed a visual directional-choice task (Fig. 4, above). To do this, the right index finger was positioned on a central sensor with a green light. After a random interval of a few seconds, a red light turned on randomly in one of three sensors placed 10 cm away from the green-light sensor. The patients were instructed to move their hand as quickly as possible in order to reach the target red-light sensor. As shown in Fig. 4 (below), the stimulator was turned off several times (at 4 and 2 weeks) before the test session.

Each time the velocity of movement was measured just before the stimulator was turned off and 30 min later. Thus the measurement at 30 min reflects the worsening of motor performance. On the day of the experimental session, the stimulator was maintained on but the patients were told that it had been turned off, so as to induce negative expectations of motor performance worsening (nocebo procedure). It can be seen that, although the stimulator was on, motor performance worsened and mimicked the worsening of the previous days. In Fig. 4, it can also be seen that this nocebo bradykinesia could be prevented completely by verbal suggestions of good motor performance (placebo procedure). Therefore, as occurs for pain, in this case also, motor performance can be modulated in two opposite directions by placebos and nocebos, and this modulation occurs on the basis of positive and negative expectations about motor performance.

These findings have been confirmed very recently by Mercado et al. (2006) who also found a dissociation of the effects in tremor, rigidity and bradykinesia. In fact, these authors found significant effects for bradykinesia, but not for tremor and rigidity. On the basis of the studies by Pollo et al. (2002), Benedetti et al. (2003b) and Mercado et al. (2006), bradykinesia appears to be a symptom that is more sensitive to verbal suggestions than tremor and rigidity. Certainly, more studies are needed to clarify this point, as in at least two studies (Pollo et al., 2002; Benedetti et al., 2003b) only bradykinesia was tested, thus no detailed information is available for the other symptoms.

Due to ethical limitations, no neurobiological mechanism is known for this nocebo bradykinesia. Unfortunately, it will not be easy to devise experimental protocols in these patients to search for its neural mechanisms, as this would require some unnecessary worsening of the parkinsonian symptoms. It is important to point out that in the experiments described above the procedure of turning the stimulator off for a short period of time represents routine clinical practice to test several parameters of stimulation.

OPEN VERSUS HIDDEN INTERRUPTION OF TREATMENTS

One of the most interesting experimental approaches that emphasizes both the importance of positive and negative expectations and their clinical impact is represented by the open–hidden paradigm (Colloca et al., 2004; Colloca and Benedetti, 2005). The open (expected) administration of a medical treatment consists of the administration of a therapy by a doctor who tells the patient that his/her symptoms will improve, according to routine clinical practice. Therefore, in this condition, the patient expects a benefit. By contrast, the hidden (unexpected) administration consists in the administration of a therapy by a computer with the subject completely unaware that a treatment is being carried out. In this case, the patient does not expect anything. Several studies have shown that an open treatment is more effective than a hidden one, thus indicating that expectation plays a crucial role in the therapeutic outcome.

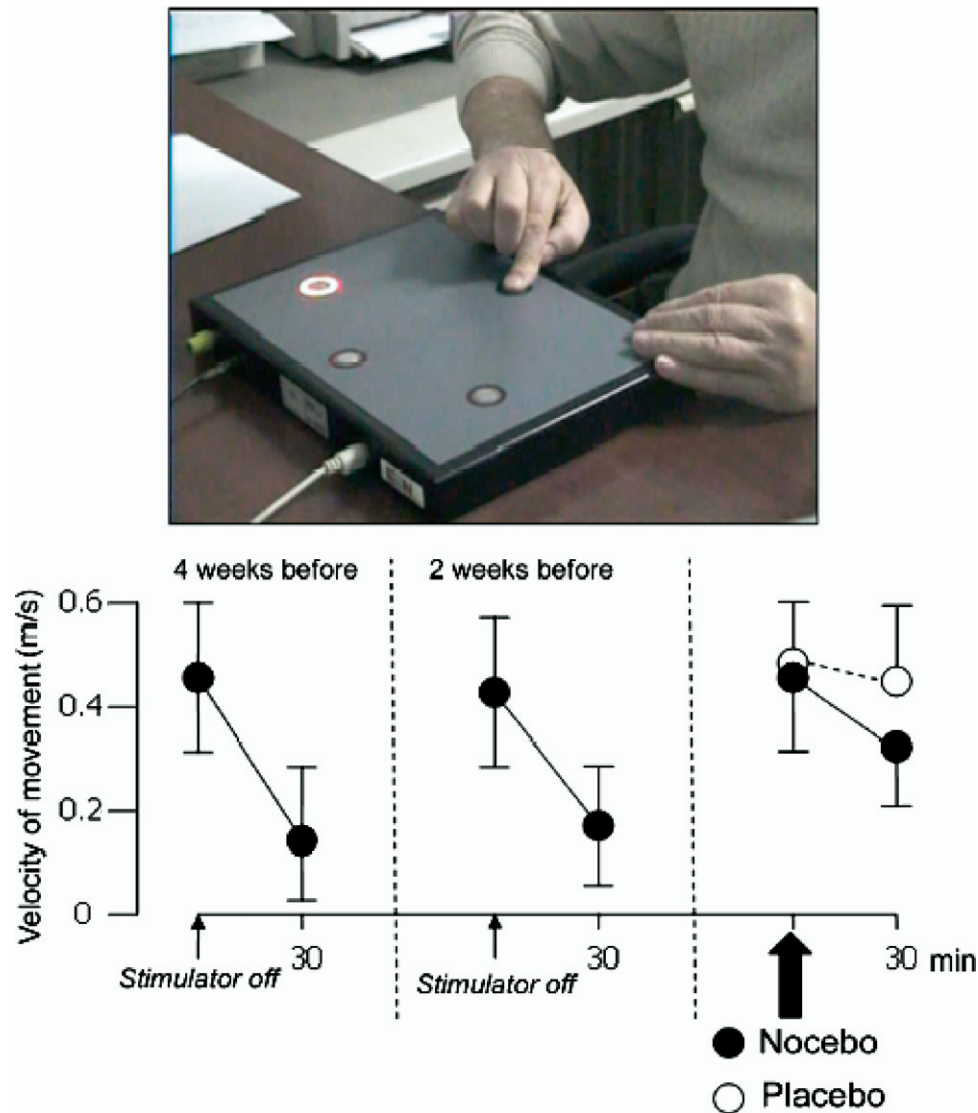


Fig. 4. Assessment of movement velocity in Parkinson patients by means of a movement analyzer. After the stimulator for deep brain stimulation had been turned off at 4 and 2 weeks before the experimental session, nocebo suggestions of clinical worsening were given but the stimulator was maintained on. Each time the velocity of movement was measured just before the stimulator was turned off and 30 min later. Thus the measurement at 30 min reflects the worsening of motor performance. Note that, despite the stimulator still being on, nocebo induced worsening. Placebo suggestions of improvement antagonized this nocebo effect completely (data from Benedetti et al., 2003b).

(Levine et al., 1981; Amanzio et al., 2001; Benedetti et al., 2003a; Colloca et al., 2004). Whereas the outcome following a hidden treatment represents the real specific effect of the treatment itself, free of any psychological contamination, the outcome following an open treatment represents the sum of the specific effect plus the psychological effect. The difference between the open and hidden treatment has been considered to represent the placebo component, even though no placebo has been given (Amanzio et al., 2001; Price, 2001; Benedetti et al., 2003a; Colloca et al., 2004).

The open–hidden approach has also proven to be useful to understand nocebo-related phenomena. In this case, open and hidden interruptions of treatments have been studied. An open interruption is preformed by the doctor who tells the patient that the treatment has been

discontinued. A hidden interruption is carried out by a computer and the patient does not know about the interruption: he believes that the therapy is still being administered.

Benedetti and collaborators (Benedetti et al., 2003a; Colloca et al., 2004) studied the effects of open (expected) versus hidden (unexpected) interruptions in at least three conditions: pain, Parkinson's disease, and anxiety. As far as pain is concerned, postoperative patients, after having received morphine for 48 h, underwent either an open or a hidden interruption of the morphine. In the open condition, the patients were told that morphine had been stopped, in the hidden condition morphine was stopped without telling the patient anything. After the interruption of morphine, the pain increase was larger in the open than in

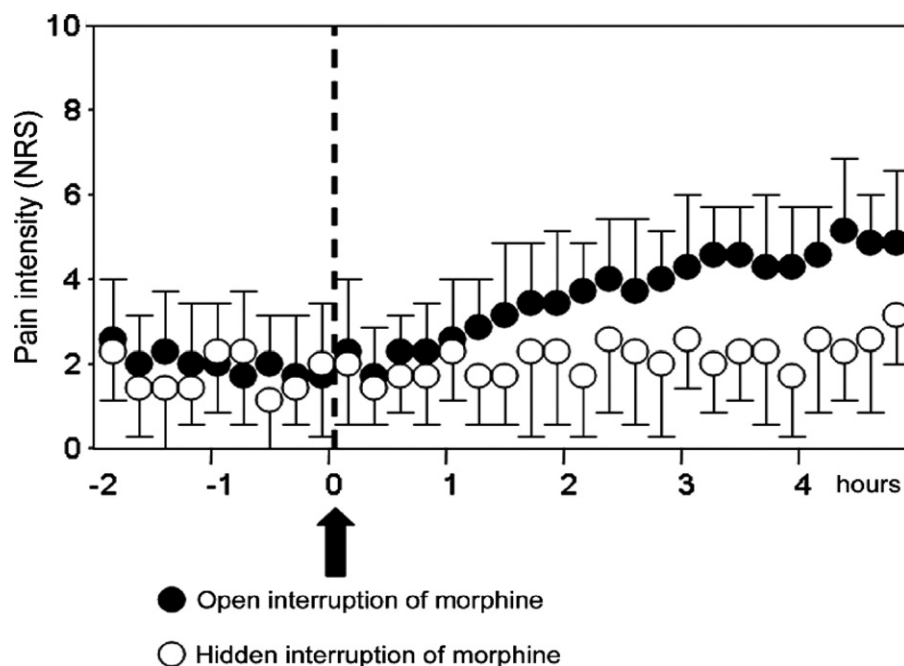


Fig. 5. Open versus hidden interruption of a morphine treatment. The broken line shows the time of morphine interruption. Note the early relapse of pain in the open group but not in the hidden one, thus indicating that the relapse in the open condition is a psychological effect. NRS=numerical rating scale (data from Benedetti et al., 2003a and Colloca et al., 2004).

the hidden condition (Fig. 5). At 10 h from morphine interruption, more patients of the open group requested further painkillers than the patients of the hidden group. Therefore, the hidden interruption of morphine prolonged the post-interruption analgesia. The best explanation of this difference is that in the open condition, fear and negative expectations of pain relapse played a crucial role.

A similar effect was found in Parkinson patients who were undergoing deep brain stimulation (Benedetti et al., 2003a; Colloca et al., 2004). The stimulator was turned off either overtly or covertly and the velocity of hand movement assessed. The open interruption induced a decrease of movement velocity at 30 min which was larger than the hidden interruption (Fig. 6). Similarly, in postoperative patients who had undergone diazepam administration for 48 h, the infusion was stopped either overtly or covertly and their level of anxiety tested every 4 h. In the open condition, anxiety increased after 4 and 8 h whereas in the hidden condition it changed neither at 4 nor at 8 h (Fig. 7).

Although no biological mechanism is known for these effects, these clinical observations are extremely important to understand how expectations affect the therapeutic outcome. Furthermore, these clinical data may be integrated with those described above, in which the neuroanatomy and biochemistry of negative expectations and nocebo effects are better known. In fact, a hidden interruption is basically an unexpected interruption whereby negative expectations of symptom relapse are absent. In these circumstances, patients believe that the treatment is still on, thus their expectation of clinical benefit is still active. Conversely, the open interruption basically tells the patient that

a symptom relapse may be occurring shortly, so that anxiety about the impending relapse may be critical in this case.

The clinical impact of these findings is important. Although doctors should strive to enhance the patient's knowledge about a therapy, it is interesting to note that this is advantageous only when the therapy is being administered. By contrast, if the therapy has to be interrupted, such awareness might be deleterious for the patient. In fact, the open interruption of morphine, deep brain stimulation and diazepam produces a greater worsening of the symptoms compared with a hidden interruption. Therefore, if the patient is told that a treatment is going to be stopped, a nocebo-like phenomenon may occur or, in other words, the expectation of worsening may counteract the beneficial effects which are present after the treatment interruption.

CONCLUSIONS

The concept of nocebo and nocebo-like effects is related to that of negative expectation of an outcome. Unfortunately, little is known about its neurobiology, although some neuroanatomical and neurochemical mechanisms have been unraveled for pain. In particular, anticipatory anxiety about the impending pain has been found to play an important role and to activate the CCKergic systems which, in turn, facilitate pain transmission. By taking the findings on nocebo and those on placebo together, the placebo–nocebo phenomenon represents a nice example of how positive and negative expectations about pain affect different neurochemical systems, that is, endogenous opioids and CCK. More specifically, verbal sugges-

tions of pain decrease activate endogenous opioids (Amanzio and Benedetti, 1999; Zubieta et al., 2005) whereas suggestions of pain increase activate CCK (Benedetti et al., 2006). The balance between these two systems may play a key role in the course of many diseases, and may represent a point of either vulnerability or strength in some patients. For example, high nocebo responses may interfere negatively whereas low nocebo responses may interfere positively with both the natural course of a disease and the response to a treatment.

In natural situations outside the experimental setting, nocebo and/or nocebo-like effects can be seen after negative diagnoses, in which the perceived symptom may increase because of negative expectations about the course of the disease. Likewise, nocebo and/or nocebo-related effects may occur when distrust toward medical personnel and therapies are present. In this latter case, unwanted effects and side effects may occur as the result of negative expectations (Flaten et al., 1999; Barsky et al., 2002), and these may reduce, or even conceal, the efficacy of some treatments. It is also worth mentioning some other natural nocebo situations, such as health warnings in western societies and black magic in other societies. In the first case, negative health warnings by the mass media may have an important impact on many individuals, while in the second

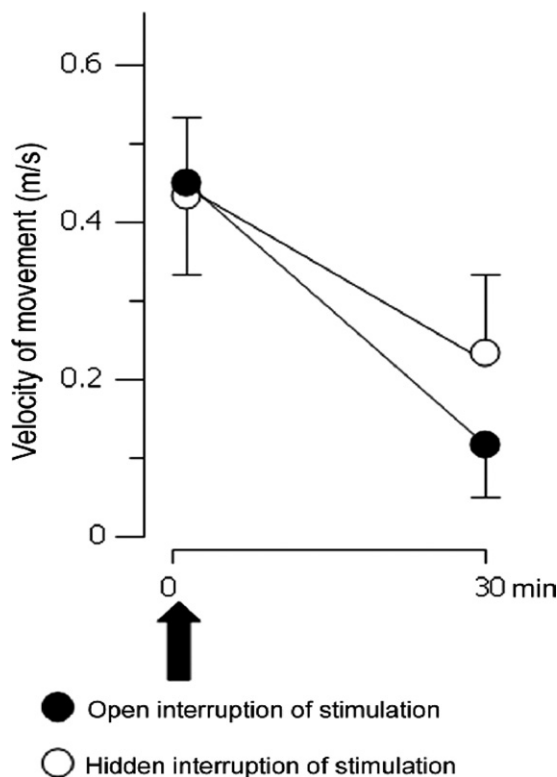


Fig. 6. Velocity of movement decrease 30 min after open or hidden interruption of deep brain stimulation. A hidden interruption induces less worsening than an open one. The open–hidden difference represents the psychological component of the worsening (data from Benedetti et al., 2003a).

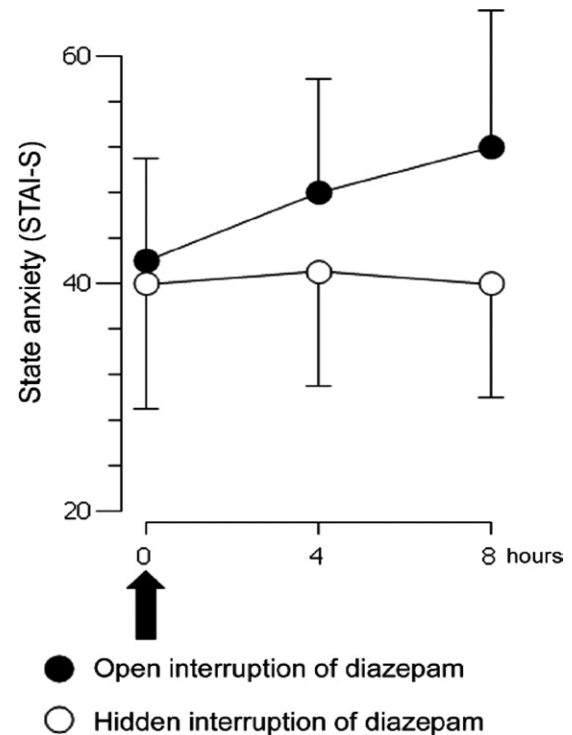


Fig. 7. Anxiety scores (STAI-S) at 4 h and 8 h after open or hidden interruption of a diazepam therapy. A hidden interruption does not induce any relapse of anxiety, which indicates that the relapse after the open interruption is a psychological effect (data from Benedetti et al., 2003a).

case some negative expectation-inducing procedures, like voodoo magic, may lead to dramatic outcomes.

Pain is the only condition in which we are beginning to understand some basic mechanisms of the nocebo effect, but certainly the mechanisms of nocebo phenomena in other conditions are worthy of extensive investigation in future research. This ultimately will lead to both clinical and social implications.

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