Placebo/Nocebo: The "Biochemical" Power of Words and Suggestions

The last two decades have produced a constantly growing body of evidence that the experience of pain, as well as other senses, is created by the brain rather than by sensory input alone. The neuromatrix concept suggested by Melzack in the 1990s[1] summarizes the way in which we understand pain today. Namely, that pain is produced by the output of the neural network in the brain rather than by sensory input evoked by injury, that the output pattern is determined by multiple influences (the somatic sensory input being only one of them), and that it is affected by top-down control. Recent studies incorporating modern technology such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) provide information about the pain neuromatrix and confirm its existence.[2,3]

In spite of the basic understanding that top-down control of sensory input plays a fundamental role in shaping our global perceptual experience, we are still far from a final understanding of the way in which emotions, cognitions, and expectations are often as powerful as (or sometimes even more than) physical stimuli in creating, or blocking, individual pain experience.

Physicians, dentists, and their patients commonly interrelate in a close, confined environment. Information sharing, clinical examinations, and basic invasive procedures are mostly performed on a one-to-one basis in a confined room where attention can hardly be distracted to other matters. In such a setting, verbal and nonverbal cues can have a profound effect on the patient's actual pain perception through eliciting placebo or nocebo effects.

The initial use of placebo in treatment was through giving the patient a dummy treatment which he or she believes is an effective therapy and expects a reduction in symptoms. Today, a wider concept is accepted in which the placebo effect includes the psychosocial context that surrounds the patient.[4] It is now understood that the mental events induced by placebo can activate mechanisms that are similar to those activated by drugs, indicating a similarity between psychosocial and pharmacodynamic effects.[5]

The psychobiological phenomenon of placebo is far from being simple. Amanzio and Benedetti[6] evoked different types of placebo analgesic effects by using cognitive expectation cues, drug conditioning, or a combination of both. The drug conditioning was carried out with either morphine or the nonsteroidal anti-inflammatory drug ketorolac. Expectation cues produced placebo responses that were completely blocked by the opioid antagonist naloxone. Also, expectation cues together with morphine, and morphine conditioning alone, induced a naloxone-reversible placebo effect. In contrast, when conditioning was done with the nonopioid ketorolac, the resulting placebo was not antagonized by naloxone, indicating that different types of placebo could be evoked (naloxone-reversible, partially naloxone-reversible, or naloxone-insensitive). Namely, cognitive factors and conditioning are balanced in different ways in placebo analgesia, and this balance is crucial for the activation of opioid or nonopioid systems. Whereas expectation triggers the endogenous opioid system, conditioning procedures activate specific subsystems. Furthermore, expectations have been found to activate not only endogenous opioids but also act on other pain-modulating networks, decrease the transmission in pain-related pathways, induce a release of dopamine in the striatum, and affect the activity of single neurons in the subthalamic nucleus.[7]

Another neuropeptide potentially involved with the placebo/nocebo effect is cholecystokinin (CCK), which is found in great concentrations throughout the central nervous system. Increased CCK has been associated with motivational loss, anxiety, and panic attacks. The close neuroanatomic distribution of CCK with opioid peptides in the limbic system suggests that there might be an opioid CCK link in the modulation and expression of anxiety or stress-related behaviors.[8]

Recent experimental evidence indicates that negative verbal suggestions induce anticipatory anxiety about the impeding pain increase, and that this verbally induced anxiety triggers the activation of CCK, which, in turn, facilitates nociceptive transmission. CCK antagonists (eg, proglumide) have been found to block this anxiety-induced hyperalgesia.[7] Thus, CCK activation can lead to the disadvantageous nocebo effect. The nocebo effect consists of delivering suggestions of negative outcomes so that the subject expects clinical worsening. Colloca et al[9] showed that nocebos can indeed produce both hyperalgesic and allodynic effects and that learning is not important in nocebo hyperalgesia compared to placebo analgesia.

Another technique widely using words and suggestions for pain management is hypnosis. Defined as "an altered state of consciousness characterized by markedly increased receptivity to suggestion,"[10] hypnosis incorporates suggestions with muscle relaxation which inevitably leads to a decrease in the subject's stress response.

Although both aim at a similar target, and broadly use words and suggestions as a tool to manage pain, hypnotic analgesia and placebo effect are not similar. While placebo analgesia is affected by expectation,[5,6,11] the effect of expectation on hypnotic analgesia is less obvious. Sharav and Tal[12] showed two components of hypnotic analgesia: one that has features similar to placebo and bears no clear relationship to hypnotic susceptibility and another that is positively related to hypnotic susceptibility. They suggest that expectation has a minimal role in producing hypnotic analgesia, a fact that distinguishes hypnotic and placebo analgesia.

Another, more practical, aspect which distinguishes the placebo/nocebo effects from hypnosis in the clinical setting is that placebo/nocebo suggestions are sometimes introduced unpremeditatedly, while hypnosis usually utilizes an "a priori" planned process. In that respect, the clinician's interpersonal communication skills can have an immediate placebo/nocebo effect on the patient's reaction to acute pain stimuli or on chronic pain treatment outcomes. Unfortunately, dental treatment is often associated with stress and anxiety, with many patients expecting to experience some level of pain during treatment. A dentist (or any caregiver) who is not fully aware of the power of words and nonverbal cues may unthinkingly introduce suggestions that lead to increased pain (nocebo). An inappropriate word, an indifferent intonation, an unexpected noise, can mistakenly be interpreted by the anxious patient as a cue of incoming pain, increase pain expectation, and lead to the unbeneficial nocebo effect. Creation of mutual trust, empathic relation to the patient's directly or indirectly expressed stress, and careful use of words can decrease pain expectation and initiate the beneficial placebo response.

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References

1. Melzack R. Pain and stress: A new perspective. In: Gatchel RJ, Turk DC (eds). Psychosocial Factors in Pain. New York: The Guilford Press, 1999:89–106.
2. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain 2005;9:463–484.
3. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron 2007;55:377–391.
4. Benedetti F, Colloca L. Placebo induced analgesia: Methodology, neurobiology, clinical use and ethics. Rev Analgesia 2004;7:129–143.
5. Colloca L, Benedetti F. Placebo as painkillers: Is mind as real as matter? Nat Rev Neurosci 2005;6:545–552.
6. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: Expectation-activated opiod systems versus condition-activated specific subsystems. J Neuorosci 1999;19:484–494.
7. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: Unraveling the mechanisms of the nocebo effect. Neuroscience 2007;147:260–271.
8. Hebb AL, Poulin JF, Roach SP, Zacharko RM, Drolet G. Cholecystokinin and endogenous opioid peptides: Interactive influence on pain, cognition and emotion. Prog Neuropsychopharmacology Biol Psychiatry 2005;29:1225–1238.
9. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain 2008;136:211–218.
10. Barber J. A brief introduction to hypnotic analgesia, In: Barber J (ed). Hypnosis and Suggestion in the Treatment of Pain. New York: Norton, 1996:5.
11. Montgomery GH, Kirsch I. Mechanism of placebo pain reduction an empirical investigation. Psychol Sci 1996;7:174–176.
12. Sharav Y, Tal M. Focused analgesia and generalized relaxation produce different hypnotic analgesia in response to ascending stimulus intensity. Int J Psychophysiol 2004;52:187–196.