Commentary

Physiological mechanisms of acupuncture: Beyond placebo?

Individuals who have chronic pain that does not respond well to conventional medicine often seek alternative treatments for which medical science does not have an adequate explanation of their effects [2]. In some quarters such treatments are viewed with suspicion, and it has been proposed that the efficacy of alternative therapies can be mostly attributed to placebo effects [9]. While scientific evidence for the effectiveness of many alternative treatments is lacking, the use of acupuncture to relieve pain has prompted a large degree of interest in the medical research community. The efficacy of acupuncture in chronic pain is inconsistent across studies. However there is enough evidence of different physiological effects to encourage research into the mechanism(s) through which acupuncture might improve pain.

Two closely linked candidate systems by which acupuncture may exert its effects are the hypothalamic–pituitary–adrenal (HPA) axis, and the endogenous opioid (EO) system. These systems are important mediators of the stress response to pain and other threatening stimuli [5], and considerable evidence implicates abnormalities in these systems in chronic pain conditions such as fibromyalgia [3], which are thought to involve psychosocial factors in their aetiology. Recent neuroimaging evidence has shown that the relationship between the neurochemical changes within the endogenous μ -opioid system [4] and the long-term pain-relieving effects of acupuncture appear to be opposite to that observed with placebo or sham treatments [17], even though treatment and sham/placebo treatments produce almost identical reductions in perceived pain. These observations suggest that acupuncture and placebo treatments, in fact, operate according to different mechanisms, with only acupuncture exerting long-term therapeutic effects on the EO system.

However, the effect of acupuncture on the HPA system is far from clear. Although cortisol release is one of the consequences of HPA system activation, different studies have shown opposite responses of cortisol release in response to acupuncture. For example, normal individuals show opposite cortisol responses to those with chronic pain conditions [11,13]. This suggests that if the HPA axis contributes to the efficacy of acupuncture, its role is more complex than simply deactivating this system. Rather the contribution may depend on the population being studied. One mediating factor may be the presence or absence of anxiety and depression, which are known to predict the onset and severity of chronic pain [8]. There is a general belief that hyperactivity of the HPA axis is associated with depression and anxiety disorders [15], an imbalance that may be expected to be corrected after appropriate therapy. This highlights the need for detailed psycho-physiological profiling of patients entering research studies that attempt to elucidate the mechanisms of new treatments.

Although research has already shown some efficacy of acupuncture in treating the pain of osteoarthritis (OA) [14], to date no one

has demonstrated a simultaneous reduction in pain symptoms and improvements in markers of HPA axis function. In a new study by Ahsin et al. [1] presented in this issue of *Pain*, the effectiveness of electro-acupuncture in the treatment of OA was examined alongside changes in the functioning of the HPA axis and EO system. The success of the treatment was measured as a reduction in the experienced pain from OA of the knee joint, relative to a sham treatment. This is the first study to show a reduction in pain, reduction in blood cortisol, and an increase in blood β -endorphin within the same cohort of patients. The study is therefore a major step forward in understanding the role of the HPA and EO systems in the effectiveness of acupuncture in chronic pain. However, unanswered questions remain, and it is hoped that the research of Ahsin et al. [1] will prompt further studies to answer these. The authors mention that these studies are consistent with previous neuroimaging studies suggesting increased EO activity in states of chronic pain [6,7]. However, the question remains as to whether the brain mechanisms of acupuncture are related to increased release of EOs or up-regulation of receptors as suggested by Harris and colleagues, or both of these on different time scales.

Although improvements in both pain and HPA/EO system function have been demonstrated, it cannot yet be established whether improvements in HPA/EO system function are causal in the efficacy of the acupuncture treatment. Indeed, it remains a strong possibility that improvements in HPA/EO system function are an epiphenomenon of reduced pain symptoms, which may be mediated by an alternative mechanism, either psychological or physiological. The role of psychological factors in mediating the therapeutic effects of electro-acupuncture cannot be underestimated, considering the extremely potent effects of placebo treatments. The study by Ahsin et al. [1] attempted to control for placebo effects using a sham treatment, but it is not clear whether a sham treatment can control for all effects related to placebo.

An important aim for future studies of the mechanisms of alternative therapies must be to control appropriately for a number of factors. Regarding placebo effects, if a perfect sham treatment does not exist or is impractical to implement, one possibility is to pre-screen study participants for the extent to which they produce a placebo response. Although the concept of a 'placebo responder' may still be controversial, there is interest in identifying such individuals for the purpose of balancing responders between treatment and placebo arms of clinical trials [10]. Preliminary evidence, in fact, suggests that placebo responses to the same treatment are highly reproducible within a group of individuals [12,16]. When investigating the mechanism of alternative treatments that could simply work by inducing a larger placebo effect than a sham treatment does, it may be more appropriate to exclude placebo responders from the trial altogether. Secondly, further and more detailed psycho-physiological assessments of patients entering a

study of treatment mechanisms would be warranted to allowing phenotyping of patients on the basis of their levels of psychological distress and baseline functioning of candidate physiological systems. Lastly, it is important to repeat the study of Ahsin et al. [1] in larger groups of patients and to show correlations between reductions in pain and changes in hormonal markers of HPA axis function. This will aid in establishing whether changes in HPA axis are causal or merely epiphenomenal in treatment efficacy.

References

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