The placebo effect in Parkinson’s disease

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The biochemical bases of the placebo effect are still incompletely known. We show here that the placebo effect in Parkinson’s disease is due, at least in part, to the release of dopamine in the striatum. We propose that the placebo effect might be related to reward mechanisms. The expectation of reward (i.e. clinical benefit) seems to be particularly relevant. According to this theory, brain dopamine release could be a common biochemical substrate for the placebo effect encountered in other medical conditions, such as pain and depression. Other neurotransmitters or neuropeptides, however, are also likely to be involved in mediating the placebo effect (e.g. opioids in pain disorders, serotonin in depression).

The word placebo is Latin for ‘I shall please’ [1,2]. Types of placebo include pills, injections and surgical procedures. It is assumed that a placebo is devoid of any specific effect for the medical condition being treated, but researchers have often been mesmerized by the positive responses of patients to these ‘inert’ interventions. This response is known as the ‘placebo effect’ [3,4]. Stewart Wolf defined this as ‘any effect attributable to a pill, potion, or procedure, but not to its pharmacodynamic or specific properties’ [5]. This is only one among a great number of proposed definitions [6,7]. At the heart of them all is the concept that a placebo must lack any specific properties. Interestingly, however, the placebo effect can be very specific [8], and this specificity depends upon the information available to the recipient [9]. For example, placebos can have opposite effects on heart rate, or blood pressure, depending on whether they are given as tranquillizers or as stimulants [8].

Hence, we should distinguish carefully between the placebo as an agent and the placebo effect. Following the principle that any treatment that provides benefit to the patient ought to be incorporated into clinical practice, we should learn to maximize the placebo effect inherent in any active treatment [10].

There is evidence to suggest that the placebo effect is related to the patient’s expectation. Two alternative theories have traditionally been proposed to explain the placebo effect [11]: (1) the mentalistic theory, according to which the patient’s expectation is the primary basis for the placebo effect, and (2) the conditioning theory, which states that the placebo effect is essentially a conditioned response. Models have been developed to support one or other of these theories [8,12–14]. For example, expectation and conditioning could activate different biochemical pathways in placebo analgesia [15,16]. Naturally, both mechanisms could contribute to the placebo effect in any given patient. One potential problem with the conditioning theory of the placebo effect is that placebo responses can occur in subjects without previous drug experience [17]. Importantly, the theories can be reconciled if, as some recent refinements of the Pavlovian conditioning theory suggest, what is learned in Pavlovian conditioning is in fact an expectation [8,18,19].

Many medical conditions are susceptible to the placebo effect [3,4]. Although a recent meta-analysis has called its importance into question [20], new evidence supporting the expectation theory of the placebo effect suggests that the studies included in this analysis might not have been optimal to address the issue (reviewed in Ref. [21]).

Pain, depression and Parkinson’s disease are among the disorders in which the placebo effect can be prominent [22–24]. This raises the possibility that the effect might be mediated by changes in neurotransmitter or neuropeptide transmission [25]. It is worth noting that patients with Parkinson’s disease often experience depression and pain [26]. Indeed, depression can precede the occurrence of motor dysfunction in Parkinson’s disease [27], suggesting that it is a primary defect (i.e. endogenous depression) rather than a consequence of chronic motor disability (i.e. reactive depression).

Kinesia paradoxica: psychologically driven dopamine release?

A remarkable phenomenon sometimes encountered in advanced Parkinson’s disease is that a patient who is usually severely impaired can perform very effective movements during a short period of time, under certain unusual circumstances (e.g. a fire). This phenomenon, called kinesia paradoxica (or paradoxical kinesia), has long puzzled neurologists [28]. Two theories have been put forward to explain it. According to one, the motor activity in kinesia paradoxica could be mediated by non-dopaminergic system(s) (i.e. neural pathways mostly activated by emergency situations or stress). Alternatively, the damaged nigrostriatal dopamine system of patients with Parkinson’s disease could be activated in particular situations, either by environmental stimuli or by the psychological response to such stimuli. According to the latter theory, kinesia paradoxica would reflect a substantial, psychologically induced release of endogenous dopamine. In keeping with this notion, animal experiments have shown that, in the presence of arousing stimuli, dopaminergic neurons of
the substantia nigra increase their firing rate and release dopamine in the striatum [29–31]. Moreover, when compared to control subjects, patients with Parkinson’s disease show verbal kinesia paradoxica – an increase in word counts and discourse duration when talking about emotional experiences [32]. However, animal models of kinesia paradoxica seem to favour non-dopamine-mediated mechanisms [33,34]. For example, rats rendered akinetic by intraventricular injections of 6-hydroxydopamine and treated with a combination of dopamine D1 and D2 receptor antagonists were still able to swim and escape from an ice bath [33]. It remains unclear, however, whether these animal models are appropriate to study the kinesia paradoxica encountered in patients with Parkinson’s disease [25].

The placebo effect in Parkinson’s disease: results of clinical trials
Although some clinical trials have shown only a modest placebo effect in Parkinson’s disease (e.g. see Ref. [35]), there is ample evidence for a strong placebo effect in this disorder. Thus, in a double-blind trial of pergolide as a treatment for Parkinson’s disease, Diamond and colleagues [36] found a significant improvement with respect to baseline in both the pergolide-treated group (17% improvement after four weeks and 30% after 24 weeks) and the placebo group (16% improvement after four weeks and 23% after 24 weeks). In this study, there was no significant difference between the pergolide-treated and placebo groups.

Shetty and colleagues [37] have recently reviewed 98 relevant articles that were published between January 1969 and April 1996, finally selecting 36 that satisfied their inclusion criteria. Twelve of these articles reported an improvement following placebo treatment in Parkinson’s disease. The magnitude of the improvement was 9–59% of that seen in the active drug group. Retrospective analysis of the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) study found a slightly lower percentage of patients experiencing improvement during placebo therapy (21%). More recently, Goetz and colleagues [38] reported that 14% of the patients enrolled in a six-month, randomized, multicentre, placebo-controlled clinical trial of ropinirole monotherapy achieved a 50% improvement in motor function while on placebo treatment. In this study, all domains of parkinsonian disability were subject to the placebo effect, but bradykinesia and rigidity tended to be more susceptible than tremor, gait or balance.

The importance of including a placebo group when investigating the efficacy of surgical treatments (e.g. transplantation) for Parkinson’s disease has been emphasized by several authors [24]. Although the effect of an imitation operation was modest in some studies [39], others reported placebo improvement of the same magnitude as that seen in the transplant group [40].

Several factors could explain the differences in the magnitude of the placebo response among different trials. These include differences in the information given to patients and differences in group characteristics or surgical procedures [21]. Importantly, it should be emphasized that the only two studies to have focused on the placebo effect in Parkinson’s disease both found the effect to be strong [37,38].

Dopamine, expectation and reward
The dopaminergic system has long been implicated in reward mechanisms [41,42]. Animal experiments have shown that the midbrain dopaminergic cell groups A8, A9 and A10 are activated by primary rewards, reward-predicting stimuli and novel stimuli [43,44]. Although three major dopamine-containing pathways (the nigrostriatal, mesolimbic and mesocortical pathways) participate in these responses, the projection to the nucleus accumbens has received the greatest attention [41,42]. Release of dopamine in the nucleus accumbens occurs during intracranial self-stimulation, a paradigm in which an animal repeatedly presses a lever to electrically stimulate its own dopaminergic projections. This behaviour has been associated with the rewarding properties of dopamine release. Most drugs of abuse (including cocaine, amphetamine, opioids, alcohol and nicotine) are characterized by their ability to increase dopamine levels in the nucleus accumbens. Indeed, the basis of drug dependence seems to be related to the rewarding experience of dopamine release [45]. Interestingly, there is an emerging concept that several human behavioural disorders, including drug-seeking behaviour, might be related to what has been called the ‘reward deficiency syndrome’ [46–48]. Individuals with this syndrome are thought to search for ‘unnatural rewards’ to compensate for an intrinsic reward deficit; that is, they seek unnatural stimulation of dopamine release to compensate for hypoactive dopamine-mediated signalling in their nucleus accumbens.

A crucial aspect of the reward theory that remains unclear is whether dopamine release occurs in relation to the reward itself (i.e. to the perception of the reward) or to the expectation of the reward. In an elegant experiment using the intracranial self-stimulation paradigm, Garris and colleagues [49] provided evidence that it is the expectation of the reward that triggers dopamine release in the nucleus accumbens. This is in keeping with previous experiments showing that dopaminergic neurons are activated after stimuli that predict a reward [44]. We hypothesized that, if the expectation of a reward triggers dopamine release, not only in the nucleus accumbens but also in the nigrostriatal pathway, the placebo effect in patients with Parkinson’s disease could be related to the expectation of clinical benefit, and could be mediated by the release of dopamine in the striatum [50].
PET study: dopamine release in response to placebo treatment in Parkinson’s disease

Using PET with \( ^{11}C \)raclopride (RAC), we found that patients with Parkinson’s disease release substantial amounts of dopamine in the dorsal striatum (i.e. caudate and putamen) in response to subcutaneous injection of saline (Fig. 1) [50]. In this paradigm, changes in RAC binding between baseline and post-activation states (in this case, in response to placebo injection) represent a change in synaptic dopamine levels, reflecting the release of endogenous dopamine. Placebo-induced changes in striatal RAC binding potential (BP) (17% in the caudate nucleus, 19% in the putamen) (Fig. 2) were of a similar magnitude to those obtained after therapeutic doses of levodopa or apomorphine [50,51]. Indeed, the magnitude of the placebo-induced change in RAC BP in Parkinson’s disease patients was comparable to that obtained in healthy volunteers after amphetamine administration [52]. The effect showed a slight increasing rostrocaudal gradient, in contrast to the magnitude of dopamine loss in Parkinson’s disease, which is maximal in the posterior putamen. All patients showed a biochemical placebo effect (i.e. changes in RAC BP) but only half reported clinical benefit in motor function after placebo administration. Interestingly, the estimated amount of dopamine release was greater in those patients who perceived a placebo effect than in those who did not (22% and 12% decreases in RAC BP in the caudate nucleus, respectively; 24% and 14% decreases in the putamen, respectively) (Fig. 2). Based on the known relationship between dopamine levels in the putamen and motor function, we concluded that the placebo effect in Parkinson’s disease was triggered by the expectation of reward (i.e. the expectation of clinical benefit). This idea was confirmed when we analysed placebo-induced changes in the ventral striatum (nucleus accumbens). This region displayed a decline in RAC binding similar to that seen in the caudate and putamen. However, in contrast to results from the dorsal striatum, the magnitude of placebo-induced changes was not significantly different between patients who experienced clinical benefit and those who did not (R. de la Fuente-Fernandez et al., unpublished). Because the perception of clinical benefit must be rewarding, this finding suggests that dopamine is released within the ventral striatum in relation to the expectation of reward (i.e. the expectation of clinical benefit) rather than the reward itself (i.e. the perception of clinical benefit).

Controlling for confounding factors

As noted earlier, dopaminergic neurons are activated not only in relation to reward, but also in response to novel stimuli [43,44]. Hence, one could argue that our results reflect the novelty of the test situation. To address this, and other, potential issues, we studied a second group of patients with Parkinson’s disease (matched with the first for age and severity of parkinsonism) in an open fashion (i.e. without placebo intervention), as a control group. We found no differences in placebo-free, open baseline RAC BP between the patients described above and this second control group (Fig. 3). It could also be argued that the placebo-induced changes in RAC BP might be secondary to stress associated with the subcutaneous injection itself. If this were so, both placebo-tested...
and placebo-free (control) groups should have a similar degree of change induced by subcutaneous injections of apomorphine. However, this was not the case, and RAC BP values were lower in the placebo group than in the open, placebo-free control group for each dose of apomorphine (Fig. 4). These observations strengthen the view that the changes in RAC BP were a true reflection of the placebo effect and not a manifestation of either novelty or stress-induced dopamine release.

Conclusions and implications

The power of placebos to alleviate a great number of medical conditions has long been recognized [3,4]. Parkinson’s disease is among the disorders in which the placebo effect can be substantial [24,36–38,40], and PET studies have indicated that the placebo effect in Parkinson’s disease is related to the release of dopamine in the striatum [50]. Other factors can also contribute to increased dopamine-mediated neurotransmission in response to placebo treatment. For example, Guttmann and colleagues [53] have recently shown placebo-induced downregulation of the dopamine transporter. Interestingly, the nucleus accumbens is also susceptible to placebo-induced dopamine release in Parkinson’s disease, supporting the notion that placebos can activate reward mechanisms.

Dopamine, which is sometimes known as the ‘pleasure molecule’ [47], could potentially be involved in the placebo effect encountered in other medical conditions, such as pain and depression [21]. For example, there is structural, electrophysiological and biochemical evidence for opioid–dopamine interactions in the mesolimbic and mesocortical pathways [54]. This provides a morphological substrate to explain the opioid-induced release of dopamine in the nucleus accumbens. Indeed, enhanced activity of dopamine in the nucleus accumbens seems to play a role in analgesia [55]. Alternatively, the release of endogenous endorphins in placebo analgesia [56] could be modulated by dopamine-mediated mechanisms [57].

Finally, placebos could also be efficacious in long-term substitution programmes for the treatment of drug addiction [5]. Most drugs of abuse (including cocaine, amphetamine, heroin, alcohol and nicotine, to name but a few) release dopamine in the nucleus accumbens, and such dopamine-mediated activation seems to be related to the dependence properties of these drugs [58,59]. We have seen that placebos can induce release of dopamine in the nucleus accumbens. Indeed, there is evidence to suggest that placebos can be addictive, causing withdrawal symptoms when treatment is discontinued [2,5]. There are reports of successful salinic substitution for the active drug in morphine addicts [60], and methadone substitution programmes for heroin addicts can also benefit from the use of placebos [61]. Although there is the potential for placebo addiction, a reduction in the use of illicit drugs would represent a major achievement in terms of health and social safety.