Available online at www.sciencedirect.com
SCIENCE DIRECT®
Respiratory Physiology & Neurobiology 152 (2006) 340–348
RESPIRATORY PHYSIOLOGY & NEUROBIOLOGY
www.elsevier.com/locate/resphysiol

Mechanisms of the placebo effect of sweet cough syrups☆

Ronald Eccles*

Common Cold Centre, Cardiff School of Biosciences, Cardiff University, Cardiff CF10 3US, UK

Accepted 7 October 2005

Abstract

The review discusses the large placebo effect associated with cough medicines and speculates on the observation that most cough medicines are formulated as sweet syrups rather than capsules or tablets. The review proposes that the major benefit of cough medicines for treatment of cough associated with common cold is related to the placebo effect rather than the pharmacological effect of an active ingredient. The placebo effect is discussed in terms of physiological effects of cough syrups associated with the taste of the medicine and true placebo effects associated with belief in the therapy. The idea is developed that a sweet taste may modulate cough at the level of the nucleus tractus solitarius, possibly by influencing the production of endogenous opioids.

Keywords: Cough; Placebo effect; Sugar; Endogenous opioids

1. Introduction

Cough associated with common cold is one of the most common disorders, especially in children, who suffer on average from 7–10 colds a year (Johnston and Holgate, 1996). It is therefore not surprising that the UK directory of over the counter (OTC) treatments for common ailments lists 60 different medicines for the treatment of cough (OTC, 2003/2004). What is surprising is that reviews on clinical trials that investigate the efficacy of cough medicines conclude that these medicines are in general little more effective than placebo treatment (Schroeder and Fahey, 2001; Eccles, 2002; Schroder and Fahey, 2002). In clinical trials on the efficacy of cough medicines up to 85% of the reduction in cough is associated with the placebo treatment and the active pharmacological component of the medicine only contributes 15% of the reduction in cough (Pavesi et al., 2001; Eccles, 2002). There is no doubt that treatment with an OTC cough medicine is associated with a reduction in cough severity, but the efficacy of the cough medicines appears to be more related to the benefits of a placebo effect rather than any pharmacological effect of the medicine.

The placebo effect has now become an active area of research, rather than simply a control treatment, and there is much interest in harnessing the placebo effect for the treatment of disease, rather than view-

☆ This paper is part of the Special Issue entitled "Cough and its Regulation", guest-edited by John G. Widdicombe and Bradley J. Undem.

* Tel.: +44 29 20874102; fax: +44 29 20874093.
E-mail address: eccles@cardiff.ac.uk.

1569-9048/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.resp.2005.10.004

ing the placebo effect as a nuisance in clinical trials (Benson and Friedman, 1996). The number of publications on the placebo effect has increased fivefold in the last 20 years (pubMed, 2005) and several text books on this topic have been published in the last few years (Harrington, 1999; Moerman, 2002; Evans, 2003), including a book published by the British Medical Journal (Guess et al., 2002), which indicates the interest in this area in mainstream medicine. This review will discuss the effects of placebo on cough associated with common cold.

2. Historical aspects of the placebo response

The term 'placebo' originates as a latin term in the Catholic vespers for the dead, and means 'I shall please' (Harrington, 1999). The medical term 'placebo' refers to a sham treatment (sugar pills or inert tonic) that the physician uses to merely 'please' or placate an anxious patient. In modern clinical terms, 'placebo' refers to a control treatment in a clinical trial that is used to control for all the variables except the pharmacological effect of a medicine. In the history of medicine a wide range of treatments were used to treat cough and the use of these medicines was based mainly on the physicians opinion and not related to any scientific evidence of efficacy. The 1899 edition of the Merck's Manual of the Materia Medica, that lists all treatments for the practising physician, gives 61 treatments for cough, including carbolic acid, alcohol, cannabis indica, creosote, morphine, potassium bromide, sandalwood oil and zinc sulphate and describes cod-liver oil as the most useful of all remedies in cough. In the long list of cough medicines in the Merck's Manual it appears that it is the sensory impact of the medicine such as its' foul taste that is important for its efficacy rather than any pharmacological effect. In contrast the 2005 edition of the British National Formulary for British physician lists only three cough suppressants, dextromethorphan, codeine and pholcodine. The great reduction in the number of treatments for cough and indeed most other diseases has resulted from the need for science-based evidence to demonstrate that the medicines are more effective than a placebo control treatment. The first use of placebo control in a clinical trial is reported in a clinical trial on the efficacy of patulin (a form of penicillin antibiotic) in the treatment of common cold (Anon, 2004). After some small and uncontrolled studies, patulin was hailed as a cure for the common cold but the results of the controlled clinical trial in 1944 clearly demonstrated that patulin was no more effective in treating colds than a matched placebo control medicine. Since the introduction of double-blind placebo controlled clinical trials it has been deemed clinically important to demonstrate that any medicine has greater efficacy than a control placebo medicine. In this age of scientific, evidence-based research, the placebo effect was viewed more as a nuisance to the clinical investigator and the pharmaceutical industry rather than as being beneficial for the patient. However, a change of attitude has occurred and this change probably starts with the publication of an article by Beecher in 1955 entitled 'The powerful placebo' (Beecher, 1955). Beecher reported that a real therapeutic benefit could be found with placebo treatment for many diseases in 35% of patients, and he reported that in 36% of patients cough was satisfactorily relieved by placebo treatment. Although Beecher's 1955 publication on the placebo effect has been criticised (Kienle and Kiene, 1997) it can be thought of as a turning point in the way the scientific and clinical communities viewed placebos.

Research in the last decade has been successful in linking the generation of endogenous opioids to the placebo effect, especially in the analgesic effects of placebo treatment (Sauro and Greenberg, 2005). The pendulum of scientific opinion has now swung from denigrating the placebo and the problematic placebo effect, to praising the placebo effect, and this has led to an increased interest in many forms of complementary therapy such as acupuncture, aromatherapy and homeopathy (Mills, 2001) and in treatments that rely solely on belief rather than any medical intervention, such as prayer (Astin et al., 2000).

3. Magnitude of the placebo response in cough studies

In most placebo-controlled clinical trials on cough medicines for the treatment of cough associated with common cold, the effect of placebo treatment on cough is almost as great as that caused by the active treatment. A literature survey on placebo controlled clinical trials for cough associated with common cold has reported

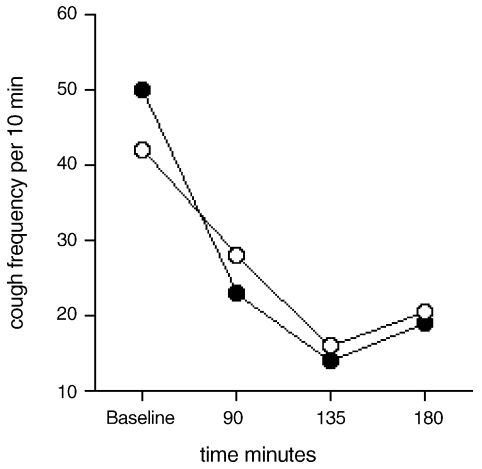

Fig. 1. Median cough frequency (per 10 min) for patients with cough associated with common cold. Immediately after the baseline measurement (0 min) patients were treated with either; a single dose of 30 mg dextromethorphan powder in a hard gelatin capsule (round symbols, $n = 21$), or a matched placebo capsule containing lactose powder (square symbols, $n = 22$) (Lee et al., 2000).

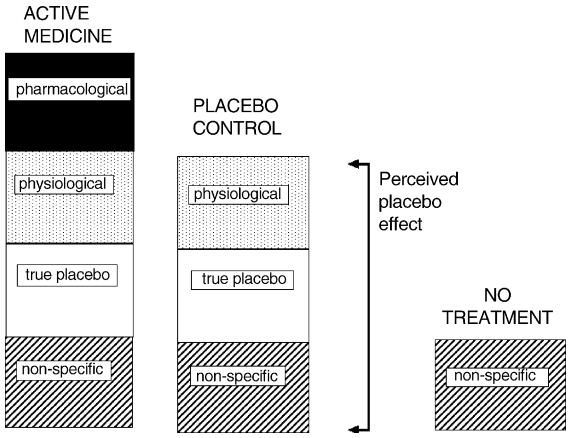

Fig. 2. Components of a cough medicine. The efficacy of a cough medicine can be attributed to at least four effects; pharmacological, physiological, true placebo and non-specific effects. The overall placebo response measured in clinical trials can be considered as a 'perceived' placebo effect that is made up of three effects; physiological, true placebo and non-specific effects.

that the placebo response varied from 56% up to a maximum of 105% of the active treatment response, with a mean of 85% (Eccles, 2002). The results from one of the studies (Lee et al., 2000) are illustrated in Fig. 1. In this study, the reduction in cough frequency following treatment with a single dose of cough medicine (30 mg dextromethorphan in capsule form) appears impressive, until it is compared with the placebo response, which is almost identical in magnitude and time course. This type of placebo response is typical of clinical trials on cough and it is often very difficult to demonstrate any benefit of a cough medicine above that of the placebo treatment.

4. How do cough medicines work?

Several factors contribute to the overall change in cough associated with treatment with a cough medicine. The changes in cough frequency associated with treatment with an antitussive medicine, such as a sweet cough syrup containing dextromethorphan, can be attributed to at least four different effects; a pharmacological effect, a physiological effect, a true placebo effect, and a non-specific effect as illustrated in Fig. 2. These four effects of treatment are discussed below. This classification of the different components of the placebo response is an extension of the ideas put forward by Ernst and Resch (1995). The classification was first described by the author in 2003 (Eccles, 2003). Ernst and Resch (1995) refer to the overall placebo effect measured in clinical trials as the 'perceived placebo effect' and propose that the perceived placebo effect may be considered as two components; a 'true placebo effect' and other 'non-specific effects' such as natural recovery from the disease and regression of symptom measurements towards the mean. In the present classification of the placebo response the 'physiological' effect is put forward as differing from the 'pharmacological effect' of the treatment as it is included in the 'perceived placebo effect' and separated from the 'non-specific effects' as discussed below. This classification is put forward for discussion and it is not at present generally used in the literature on placebo effect.

4.1. Pharmacological effect

The pharmacological effect of treatment with a cough medicine is related to the active ingredient of the medicine, such as codeine or dextromethorphan. The pharmacologically active ingredient has a high affinity for a specific pharmacological receptor, such as the interaction of codeine with opioid receptors. Slight

changes in the molecular structure of the active ingredient may have marked effects on its affinity with the receptor and its biological activity. The pharmacological effects of the opioids morphine and codeine are reported to be due to stimulation of μ-opioid receptors in the cough control areas of the brainstem (Reynolds et al., 2004). Opioid receptors have also been located in the periphery but their ability to inhibit cough by a peripheral mechanism is debatable (Reynolds et al., 2004).

In clinical trials on cough medicines, it is the pharmacological effect of the medicine that is under investigation, and any other effects of the treatment are controlled by comparison with the effects of a placebo medication that is identical in appearance, colour taste, etc. with the active medication but does not contain the pharmacologically active ingredient. The pharmacological effect of a medicine is measured by subtracting the effects of the placebo control from those of the active medicine as illustrated in Fig. 2.

4.2. Physiological effects

The physiological effects of treatment are the effects of the treatment that may be initiated by the physical properties of the medicine that are perceived by the patient, such as taste, smell, viscosity, acidity, temperature, texture, etc. These properties are related to the physical and chemical properties of the medicine and they influence the magnitude of the placebo effect through sensory information about the nature of the treatment. The active pharmacological ingredient of the cough medicine may also contribute to the physiological effects of the medicine by having a bitter taste or a distinctive smell. The term 'physiological effect' is used to support the idea that physical properties of the medicine may stimulate several sensory pathways, and the overall 'sensory impact' may enhance the placebo effect of the medicine in various ways by influencing the psychological response to the medicine and by triggering reflexes such as salivation, etc.

A physiological effect on cough may be initiated by sensory stimuli such as the sweet or bitter taste of the medicine triggering reflex salivation and the secretion of mucus in the airways. Cough syrups that contain sapid substances such as sugar, honey, spicy substances such as capiscum, and bitter tasting substances such as lemon and citric acid will readily cause reflex salivation and may also promote secretion of airway mucus. In cases of dry unproductive cough the demulcent effects of a cough medicine may lubricate the pharynx and larynx and help to reduce coughing. In cases of productive cough the increase in airway secretions caused by a sapid cough syrup may increase mucociliary clearance from the airway by an expectorant effect. Gustatory rhinorroeah has been shown to occur after eating spicy foods and this observation demonstrates a link between gustation and airway secretion of mucus (Choudry et al., 1992). Some cough medicines contain capiscum which is a potent gustatory stimulus and which may also promote airway secretions. The sweet taste of cough syrups may have been traditionally used to mask the taste of bitter tasting plant extracts such as opium, but the fact that almost all modern cough medicines are formulated as sweet sapid syrups indicates that the physiological actions of the sweet syrup may contribute to the antitussive (cough suppressant) and expectorant activity of the treatment.

In the UK directory of over the counter treatments for common ailments (OTC, 2003/2004) 58/60 of the cough medicines contain a sweetner such as sucrose, glucose, honey, treacle or with children's medicines a sugar free sweetner. The sweet taste and viscous nature of the syrup, appear to be fundamental properties of cough medicines. The sweet taste may influence cough in two ways; firstly by stimulation of airway secretions as described above, and secondly by the generation of endogenous opioids (Jain et al., 2004). The viscous nature of the cough syrup may prolong the duration of the sweet taste in the mouth.

Sucrose and glucose solutions are widely used as analgesics for new born babies (Allen et al., 1996; Akcam and Ormeci, 2004) and there is some support from animal studies that that a sweet stimulus modulates the generation of endogenous opioids (Nikfar et al., 1997; Jain et al., 2004). The same term 'craving' is used to describe the intense desire for both foods such as sucrose and for a variety of drugs of abuse, and there is increasing evidence for comorbidity between drug/alcohol abuse and excessive craving or liking for sweets (Pelchat, 2002). This similarity between drug addiction and food craving has been explained on the basis that the endogenous opioid system acts as a reward mechanism for feeding and that a sweet taste causes the production of endogenous opioids (Pelchat, 2002). Much of the research in this area has been

performed on animal models and the studies indicate that opioid agonists increase feeding and antagonists decrease feeding in non-food restricted animals (Cleary et al., 1996; Kanarek et al., 2000; Colantuoni et al., 2002). Animal studies also demonstrate that the analgesic effects of sucrose may be mediated by endogenous opioids and that this action of sucrose is inhibited by morphine antagonists (Nikfar et al., 1997; Reboucas et al., 2005). Human studies are difficult to perform in this area but there is evidence that opioid antagonists reduce the consumption of sweet foods in binge eaters (Drewnowski et al., 1995).

The analgesic activity of sweet gustatory stimuli may be related to some antitussive effect as there is a close relationship between the analgesic and antitussive properties of opioids (Eddy et al., 1969). The antitussive effect of a sweet gustatory stimulus is supported by the close anatomical relationship between control of cough and gustation. The posterior third of the tongue, epiglottis, larynx and oesophagus are supplied by gustatory fibres from the vagus nerve, and the gustatory fibres synapse in the solitary nucleus of the brainstem (Martin, 1988; Bromley and Doty, 2003). Similarly, the larynx, trachea and lower airways are supplied by viscerosensory fibres from the vagus nerve, and these vagal fibres that initiate the cough reflex also relay in the nucleus of the tractus solitarius (NTS) as illustrated in Fig. 3. The rostral area of the solitary nucleus acts as a relay for gustatory fibres of the X, IX and VII cranial nerves and the caudal area is concerned with cardiorespiratory control and the initiation of cough (Martin, 1988), but these areas overlap, and it possible that gustatory information may influence cough as illustrated in Fig. 3. The close anatomical relationship between gustatory fibres and the sensory fibres that initiate cough may explain the antitussive effects of sweet cough medicines. It is interesting to note that application of crystalline sugar to the tongue has also been reported to inhibit another respiratory reflex the hiccup or hiccough (Engleman et al., 1971). If the antitussive effects of sweetners make a greater contribution to the efficacy of cough medicines than the declared active ingredient this could explain why it is so difficult to separate a sweet active syrup from a sweet placebo syrup in clinical trials on cough medicines (Paul et al., 2004; Walburn, 2004). There are at present no studies that have directly tested the hypothesis that a sweet sapid stimulus influences cough but this is an interesting area for further research, for example it would be interesting to directly compare the antitussive efficacy of tablets or capsules with a sweet syrup.

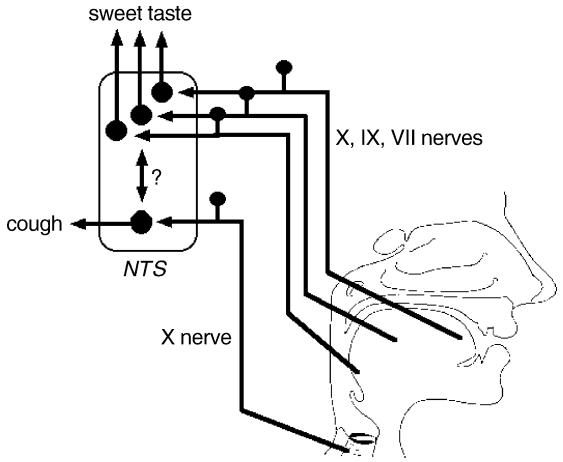

Fig. 3. Gustatory effects on cough. Gustation is mediated by branches of the VII (facial) IX (glossopharyngeal) and X (vagus) cranial nerves that supply the taste buds of the tongue. These gustatory fibres relay in the nucleus of the tractus solitarius (NTS) that also serves as the first relay for the X cranial nerves that mediate the cough reflex. It is possible that there may be some interaction between gustatory and cough pathways that influences the cough reflex, perhaps by modulating the production of endogenous opioids.

Cooling and warming agents are often added to give extra sensations to the treatment and these agents may influence the activity of cold and warm receptors. Cooling agents such as menthol are sometimes included as flavouring agents in cough medicines although menthol may also have pharmacological activity as a local anaesthetic (Eccles, 1994). The cooling properties of menthol and other cooling agents could also be considered as a pharmacological component of treatment, as there is some evidence that cooling properties are determined by interaction with a menthol type of pharmacological receptor on sensory nerves (Eccles, 1994). Although menthol is usually declared as a flavouring agent in cough medicines there is some evidence that it may have specific antitussive activity (Laude et al., 1994; Morice et al., 1994; Pavesi et al., 2001).

The physiological effect of a cough syrup may exhibit similar characteristics to a pharmacological effect, with a time course of action, peak effect, cumulative effect, and carry over effect, but at present there is no information on the pharmacodynamics of any physiological effect of treatment on cough. In the case of

cough medicines, there is likely to be a large physiological effect with a cough syrup, but little if any physiological effect with a tablet or capsule formulation.

4.3. True placebo effect

A major problem in defining the placebo effect of a cough treatment is that the effects attributed to placebo treatment often include those effects that could also be attributed to natural recovery from the disease. Some definitions of the placebo effect of treatment refer to all those effects of treatment apart from the pharmacological effects (Kienle and Kiene, 1996). But this definition is too broad as it includes any changes associated with natural recovery from the disease, and any physiological effects of the medicine.

The placebo effect (as measured in a clinical trial), has been divided into a perceived placebo effect and a true placebo effect (Ernst and Resch, 1995). This division will be used in the present discussion.

The perceived placebo effect is defined as the total effect of the placebo medicine, which includes the true placebo effect and other effects, such as any physiological effect, and non-specific effects such as natural recovery from the disease. The perceived placebo effect is normally measured in a placebo controlled clinical trial, but it is not possible to estimate the contribution of the true placebo effect to any changes in cough severity from this parameter, as the perceived placebo effect also includes the physiological effect and non-specific effect of treatment as shown in Fig. 2.

In clinical trials where a 'no treatment' group is included in the design, it is possible to control for any non-specific effects of treatment by subtracting any changes in the no treatment group from those changes observed in the placebo treatment group (Lee et al., 2005). This leaves us with a measure of any true placebo effect plus any physiological effect. In the case of cough treatments that use a tablet or capsule formulation any physiological effect of treatment will be minimal and the use of a no treatment group will allow determination of the true placebo effect. But in the case of a cough syrup there could be a large physiological effect and it will not be possible to separate this from any true placebo effect.

The true placebo effect refers to the psychological therapeutic effect of the treatment, and this will depend on many factors such as the belief in the effectiveness of the treatment and the attitude of the patient towards the therapist.

The psychological therapeutic effect attributed to the true placebo effect of treatment with a cough medicine is related to the patient's belief about the efficacy of the medicine (Evans, 2003). The degree of belief in the treatment will depend on many factors such as; the healer-patient interaction, cultural beliefs about traditional treatments, the environment in which the medicine is administered, the properties of the medicine such as taste, colour and smell, advertising and claims made about the efficacy of the medicine, the brand name of the medicine, and side effects associated with treatment that may reinforce the belief of efficacy. This list of factors that may influence the true placebo effect is not exhaustive and it illustrates how difficult it is to properly control and standardise studies on the true placebo effect.

The true placebo effect may be explained in terms of psychoneuropharmacology (Eccles, 2002), which means that the belief in the effects of the medicine triggers a distinct nervous pathway with its own neurotransmitters that can be influenced by pharmacological intervention. The true placebo effect of cough medicines may be related to the generation of endogenous opioids, as a similar explanation for placbo analgesia has been proposed (Fields and Price, 1999). If the true placebo effect on cough is mediated by the generation of endogenous opioids then this effect should be inhibited by pharmacological intervention with opioid antagonists. The analgesic effect of placebo treatment has been reported to be inhibited by administration of opioid antagonists such as naltrexone (Benedetti, 1997) but at present there are no similar reports on the effects of opioid antagonists on natural cough, although there is one negative report for induced cough (Hutchings and Eccles, 1994).

4.4. Non-specific effects

"Sick people often get better". In an acute illness natural recovery may occur and this is not due to any effect of the treatment (Ernst and Resch, 1995).

Patients recruited to a clinical trial to determine the efficacy of a cough medicine are screened to determine the severity of cough, and only those patients with a high subjective score, and/or objective measure

of cough are recruited for the study. By recruiting only those patients with a severe or troublesome cough and excluding those patients with a mild cough, the population of patients on the trial is skewed towards those with a severe cough. In these circumstances the cough severity of the patients on trial is unlikely to increase during the course of the study and it is more likely that the cough severity will decrease due to the process of natural recovery. The mean measure of cough severity is likely to decline during the course of the clinical trial and this statistical effect is often referred to as "regression to mean" (Kienle and Kiene, 1996).

It is not possible to control for the effects of rest and spontaneous recovery in controlled clinical trials that involve only placebo and active treatment groups, as both these treatment groups will be affected by rest and recovery. However, if a 'no treatment' group is included in the trial design then this will allow direct comparison with the placebo treatment group and any effect of placebo above the effect of no treatment can be deemed to be caused by a 'true placebo effect' less any physiological effect (Ernst and Resch, 1995). In a study on patients with cough associated with URTI, comparing the antitussive effects of 'no treatment' versus placebo treatment, the 'no treatment' group had a 7% decrease in cough frequency compared to a 50% decrease in the placebo treatment group as shown in Fig. 4 (Lee et al., 2005). In this study, the placebo medicine was a capsule, rather than a sweet syrup, so the placebo effect cannot be explained by any physiological effect of sugar, or by rest, and it may be reasonably defined as a true placebo effect.

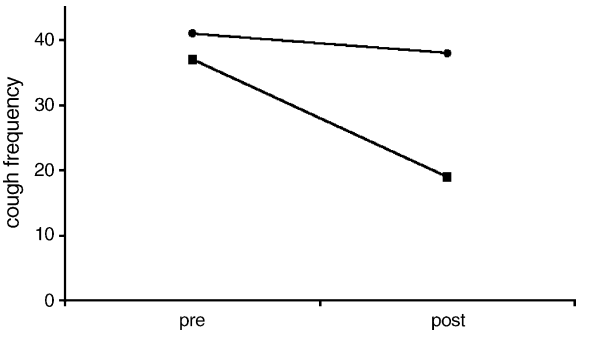

Fig. 4. Median cough frequency (per 15 min) pre-treatment and post-treatment. Round symbols represent the 'no treatment' group and filled symbols the 'placebo treatment' group. Redrawn from Lee et al. (2005).

5. Cough model

A model of the cough reflex is depicted in Fig. 5. Cough is initiated by airway irritation that is mediated by branches of the vagus nerve that innervate the

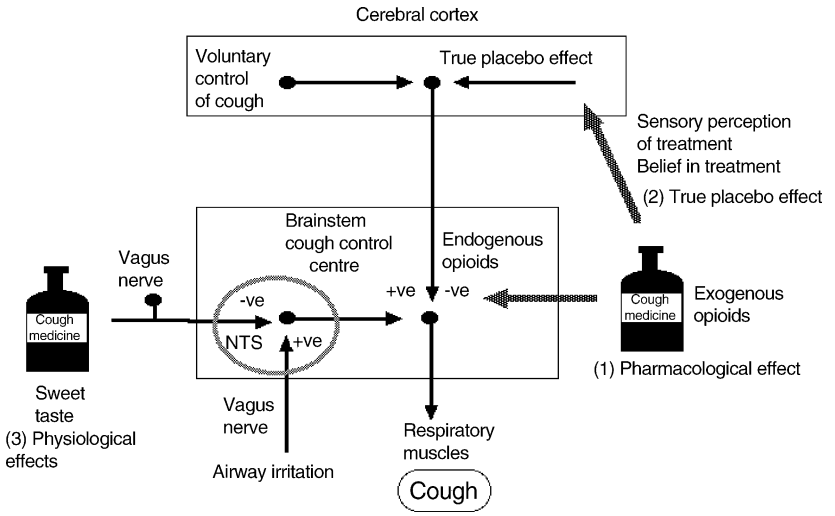

Fig. 5. Model of the control of cough. Airway irritation causes cough via a reflex pathway in the respiratory area of the brainstem. Cough is also under voluntary control from the cerebral cortex. A cough medicine may influence cough via three effects. (1) Pharmacological effect of exogenous opioids, (2) true placebo effect related to belief in the treatment and (3) physiological effect related to the sweet taste. NTS is the nucleus of the tractus solitarius.

larynx, trachea and lower airways. The cough control centre is located in the respiratory areas of the brainstem with the first neuronal relay of the vagus nerve in nucleus of the solitary tract (NTS). Cough may be initiated and inhibited by voluntary control from areas in the cerebral cortex (Lee et al., 2002). A sweet cough syrup containing an antitussive such as codeine may influence cough in three ways; (1) pharmacological effect—the codeine can be considered as an exogenous opioid that will inhibit cough at the level of the brainstem by mimicking endogenous opioid neurotransmitters, (2) true placebo effect—the belief in the efficacy of the cough medicine may initiate a true placebo effect and the generation of endogenous opioid neurotransmitters that inhibit the cough reflex, (3) physiological effect—the sweet taste of the cough syrup stimulates gustatory fibres in the tongue that may influence cough via inhibition of the cardiorespiratory area of the solitary nucleus.

6. Discussion

Placebo-controlled clinical trials have discredited most traditional cough medicines as they have usually concluded that the cough medicine is little more effective than a matched placebo medicine. This indicates that the pharmacological activity of most cough medicines is questionable but it does not mean that cough medicines are ineffective in treating cough. The major benefits of OTC cough medicines may be related to the different components of the placebo effect. If the efficacy of OTC cough medicines was related to the pharmacological activity of the medicine then there is no need to formulate the medicine as a sapid syrup rather than a tablet or capsule, as medicines such as codeine and dextromethorphan are believed to exert their antitussive action on areas of the brainstem and this will only occur after absorption into the blood stream. A tablet or capsule should be just as effective as a liquid formulation if the efficacy is solely related to the pharmacological activity of the medicine. However, the majority of cough medicines are formulated as sapid syrups and many contain only sweet substances. This indicates that the sweet taste may not be just masking a bitter ingredient but may have some role in treating cough as discussed above. Unfortunately, the focus of clinical trials on cough medicines has been to demonstrate the pharmacological activity of the medicines rather than explore any benefit attributed to a placebo effect. Since there is little evidence for a pharmacological effect on cough with antitussives such as dextromethorphan in OTC cough medicines (Schroeder and Fahey, 2001), further research on the placebo effect of cough medicines may provide new knowledge that will be of use in the treatment of cough.

7. Conclusions

The efficacy of cough medicines for the treatment of cough associated with common cold is mainly related to the non-pharmacological properties of the medicines such as the sensory impact and the placebo effects. This does not mean that the medicines are ineffective as these non-pharmacological effects can provide symptomatic relief from cough, and for an acute self-limiting disorder this maybe all that is required of a cough medicine.

References

Anon, 1944. Clinical trial of patulin in the common cold. Int. J. Epidemiol. 33, 243–246.

Akcam, M., Ormeci, A.R., 2004. Oral hypertonic glucose spray: a practical alternative for analgesia in the newborn. Acta Paediatr. 93, 1330–1333.

Allen, K.D., White, D.D., Walburn, J.N., 1996. Sucrose as an analgesic agent for infants during immunization injections. Arch. Pediatr. Adolesc. Med. 150, 270–274.

Astin, J.A., Harkness, E., Ernst, E., 2000. The efficacy of "distant healing": a systematic review of randomized trials. Ann. Intern. Med. 132, 903–910.

Beecher, H., 1955. The powerful placebo. J. Am. Med. Assoc. 159, 1602–1606.

Benedetti, F.A.M., 1997. The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. Prog. Neurobiol. 52, 109.

Benson, H., Friedman, R., 1996. Harnessing the power of the placebo effect and renaming it "Remembered Wellness". Annu. Rev. Med. 47, 193–199.

Bromley, S., Doty, R., 2003. Clinical disorders affecting taste: evaluation and management. In: Doty, R. (Ed.), Handbook of Olfaction and Gustation. Marcel Dekker, New York, pp. 935–957.

Choudry, N.B., Harrison, A.J., Fuller, R.W., 1992. Inhibition of gustatory rhinorrhea by intranasal ipratropium bromide. Eur. J. Clin. Pharmacol. 42, 561–562.

Cleary, J., Weldon, D.T., O'Hare, E., Billington, C., Levine, A.S., 1996. Naloxone effects on sucrose-motivated behavior. Psychopharmacology (Berl.) 126, 110–114.

Colantuoni, C., Rada, P., McCarthy, J., Patten, C., Avena, N.M., Chadeayne, A., Hoebel, B.G., 2002. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. Obes. Res. 10, 478–488.

Drewnowski, A., Krahn, D.D., Demitrack, M.A., Nairn, K., Gosnell, B.A., 1995. Naloxone, an opiate blocker, reduces the consumption of sweet high-fat foods in obese and lean female binge eaters. Am. J. Clin. Nutr. 61, 1206–1212.

Eccles, R., 1994. Menthol and related cooling compounds. J. Pharmacy Pharmacol. 46, 618–630.

Eccles, R., 2002. The powerful placebo in cough studies. Pulm. Pharmacol. Ther. 15, 303–308.

Eccles, R., 2003. Placebo effects of antitussive treatments on cough associated with acute upper respiratory tract infection. In: Chung, K.F., Widdicombe, J.G., Boushey, H.A. (Eds.), Cough, causes, mechanisms and therapy. Blackwell Publishing Ltd, Massachusetts, pp. 259–268.

Eddy, N.B., Friebel, H., Hahn, K.J., Halbach, H., 1969. Codeine and its alternates for pain and cough relief. Bull. World Health Organ. 40, 425–454.

Engleman, E.G., Lankton, J., Lankton, B., 1971. Granulated sugar as treatment for hiccups in conscious patients. N. Engl. J. Med. 285, 1489.

Ernst, E., Resch, K.L., 1995. Concept of true and perceived placebo effects. Br. Med. J. 311, 551–553.

Evans, D., 2003. Placebo. The Belief Effect. Harper Collins, London.

Fields, H.L., Price, D.D., 1999. Towards a neurobiology of placebo analgesia. In: Harrington, A. (Ed.), The Placebo Effect. An Interdisciplinary Approach. Harvard University Press, Cambridge, USA, pp. 93–116.

Guess, H., Kleinman, A., Kusek, J., Engel, L., 2002. The Science of the Placebo Towards an Interdisciplinary Approach. BMJ Books, London.

Harrington, A., 1999. The Placebo Effect. An Interdisciplinary Approach. Harvard University Press, Cambridge, USA.

Hutchings, H.A., Eccles, R., 1994. The opioid agonist codeine and antagonist naltrexone do not affect voluntary suppression of capsaicin induced cough in healthy subjects. Eur. Respir. J. 7, 715–719.

Jain, R., Mukherjee, K., Singh, R., 2004. Influence of sweet tasting solutions on opioid withdrawal. Brain Res. Bull. 64, 319–322.

Johnston, S., Holgate, S., 1996. Epidemiology of viral respiratory infections. In: Myint, S., Taylor-Robinson, D. (Eds.), Viral and Other Infections of the Human Respiratory Tract. Chapman & Hall, London, pp. 1–38.

Kanarek, R.B., Homoleski, B.A., Wiatr, C., 2000. Intake of a palatable sucrose solution modifies the actions of spiradoline, a kappa opioid receptor agonist, on analgesia and feeding behavior in male and female rats. Pharmacol. Biochem. Behav. 65, 97–104.

Kienle, G., Kiene, H., 1996. Placebo effect and placebo concept: a critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. Alternative Therap. 2, 39–54.

Kienle, G.S., Kiene, H., 1997. The powerful placebo effect: Fact or fiction? J. Clin. Epidemiol. 50, 1311–1318.

Laude, E.A., Morice, A.H., Grattan, T.J., 1994. The antitussive effects of menthol, camphor and cineole in conscious guinea-pigs. Pulm. Pharmacol. 7, 179–184.

Lee, P., Cotterill-Jones, C., Eccles, R., 2002. Voluntary control of cough. Pulm. Pharmacol. Ther. 15, 317–320.

Lee, P.C., Jawad, M.S., Hull, J.D., West, W.H., Shaw, K., Eccles, R., 2005. The antitussive effect of placebo treatment on cough associated with acute upper respiratory infection. Psychosom. Med. 67, 314–317.

Lee, P.C.L., Jawad, M.S.M., Eccles, R., 2000. Antitussive efficacy of dextromethorphan in cough associated with acute upper respiratory tract infection. J. Pharmacy Pharmacol. 52, 1137–1142.

Martin, J., 1988. Neuroanatomy Text and Atlas. Elsevier, New York.

Mills, S.Y., 2001. The House of Lords report on complementary medicine: a summary. Complement Ther. Med. 9, 34–39.

Moerman, D., 2002. Meaning, Medicine and the 'Placebo effect'. Cambridge University Press, Cambridge.

Morice, A.H., Marshall, A.E., Higgins, K.S., Grattan, T.J., 1994. Effect of inhaled menthol on citric acid induced cough in normal subjects. Thorax 49, 1024–1026.

Nikfar, S., Abdollahi, M., Etemad, F., Sharifzadeh, M., 1997. Effects of sweetening agents on morphine-induced analgesia in mice by formalin test. Gen. Pharmacol. 29, 583–586.

OTC Directory, 2003/2004.Treatments for common ailments. PAGB. Communications International Group, London.

Paul, I.M., Yoder, K.E., Crowell, K.R., Shaffer, M.L., McMillan, H.S., Carlson, L.C., Dilworth, D.A., Berlin Jr., C.M., 2004. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics 114, E85–E90.

Pavesi, L., Subburaj, S., Porter-Shaw, K., 2001. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough—a meta-analysis. Chest 120, 1121–1128.

Pelchat, M.L., 2002. Of human bondage: food craving, obsession, compulsion, and addiction. Physiol. Behav. 76, 347–352.

Reboucas, E.C., Segato, E.N., Kishi, R., Freitas, R.L., Savoldi, M., Morato, S., Coimbra, N.C., 2005. Effect of the blockade of mu1-opioid and 5HT2A-serotonergic/alpha1-noradrenergic receptors on sweet-substance-induced analgesia. Psychopharmacology (Berl.) 179, 349–355.

Reynolds, S.M., Mackenzie, A.J., Spina, D., Page, C.P., 2004. The pharmacology of cough. Trends Pharmacol. Sci. 25, 569–576.

Sauro, M.D., Greenberg, R.P., 2005. Endogenous opiates and the placebo effect. A meta-analytic review. J. Psychosom. Res. 58, 115–120.

Schroder, K., Fahey, T., 2002. Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults. Br. Med. J. 324, 1–6.

Schroeder, K., Fahey, T., 2001. Over-the-counter medications for acute cough in children and adults in ambulatory settings (Cochrane Review). In: The Cochrane Library, Issue 4, 2002. Oxford: Update Software.

Walburn, J., 2004. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics 114, 1370.