The placebo effect in animals

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The placebo effect has been a recognized, yet poorly understood, factor in the course and outcome of a variety of disease states in humans. The effects of placebos on the clinical course of systemic hypertension, angina pectoris, myocardial ischemia, congestive heart failure, and ventricular tachyarrhythmias have been described.[1] Other conditions for which a response to placebos has been reported include acne, asthma, colds, allergies, gastrointestinal ulcers, gastric acidity, constipation, blood cell and serum biochemical disorders, rheumatoid and degenerative arthritis, pain, and headache.[2]

Many proposed mechanisms for the placebo effect suggest the involvement of higher level cognitive capacities, such as faith, credulity, suggestibility, trust, and optimism.[3] At the least, a placebo response seems to require a recognition by the patient of the intent of treatment efforts. Because it is generally presumed that animals lack certain cognitive capacities, for example, the ability to comprehend the intent of the veterinarian's ministrations, the power of suggestion, and expectations of recovery and healing, the existence of a placebo effect in animals seems counterintuitive; however, animals have been the main subjects in experimental studies of the mechanisms of the placebo effect for the past 70 years.

The purpose of this report is to describe theories and evidence for placebo mechanisms in animals, elucidate the role of the placebo in animal health, and provide a rationale and direction for further investigation of placebo mechanisms.

Definition of Terms

Considerable debate over placebo terminology exists in the literature[4]; definitions that follow are modified from Shapiro and Shapiro.[5] A placebo is any medical intervention (including drugs, vaccinations, surgery, procedures, rituals, touch and physical manipulations, spoken words, and use of nutrition or supplementation) that has a nonspecific, psychological, or psychophysiologic therapeutic effect, or that is used for a presumed specific therapeutic effect on a patient, symptom, or illness but is without specific activity for the condition being treated. The placebo effect is the nonspecific psychological or psychophysiologic therapeutic effect induced by a placebo; the effect may be positive or negative, that is, favorable or unfavorable.

History of the Placebo

The use of placebo has been an integral part of the healing arts for centuries. The term placebo —literally "I shall please"[6]—entered the lexicon in the thirteenth century[5] and was first used as a general description for something given to "please, give pleasure, be approved, be pleasing, be agreeable, acceptable, to suit, satisfy."[7] The first documented clinical use of intentionally administered inert substances was in 1785, which coincided with the first appearance of the term placebo in a medical dictionary.[5] However, it was not until 1811 that the first approximation of the present-day usage of the term emerged; placebo was defined as "an epithet given to any medicine adopted to please rather than to benefit the patient."[8] Placebo originally was used as a derogatory term to describe the treatment provided by nonphysicians and not deliberately prescribed by physicians.[5]

In the first half of the twentieth century, recognition of the influence of the placebo effect in clinical and experimental pharmacologic trials led researchers to design new protocols to establish controls for it.[1,9] Beecher,[2] one of the first investigators to promote the inclusion of placebo controls in clinical trials,[1] developed a strategy designed specifically to prevent the patient and the physician from knowing what treatment the patient was receiving, thereby attempting to exclude expectations and beliefs of the patient and physician from evaluation of new treatments.[1] Beecher referred to this strategy as the "double unknown technique," known today as the "double-blind trial."[1] The rationale for this protocol was that the inert placebo, under double-blind conditions, would provide a control for psychological and other variables and differentiate true drug effects from placebo effects.[1,10]

With the advent of the new research methodology, the placebo moved from its role as an active therapeutic influence to its present status as a variable whose major function is to act as a control in medical research.[11] This negative connotation relegated the placebo effect to a kind of "noise in the system that has to be eliminated before the real treatment can be assessed."[11] Disdain for the placebo effect is the prevalent attitude in medicine today—it is considered a nuisance variable to be controlled and, hence, ignored.[9] In therapeutic trials, little if any attention is given to the effects, regardless of magnitude, observed in the placebo control group.[9]

Theories of Placebo Mechanisms

Although the placebo effect has been an integral part of medical treatments for centuries, it remains a poorly understood phenomenon.[12] The most fundamental assumption is that the placebo effect involves a functional interrelationship between psychological factors and physical states of the body. All proposed mechanisms suggest an interaction of brain states and somatic health processes, an interrelationship that has been extensively documented in animals.[13] However, the relationship between the placebo effect and the bodily mechanisms governing health and disease still eludes us.[5] Proposed mental components of the place-

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bo response, such as beliefs, expectations, and trust, presumably are represented at a neurobiological level,[3] yet the mechanism at the cellular level and the role of biochemical mediators remain unknown.[1]

Research on placebo mechanisms has resulted in 3 theories receiving most support[4]: classical conditioning,[1,3,4,6,12] expectancy,[4] and endogenous opiates.[1,4] In animals, a fourth theoretical mechanism for placebo action involves the effect of human contact.[14]

Conditioning—Ullman and Krasner[15] proposed the theory that conditioning effects are the basis for placebo responses.[4] In classical conditioning, an initially neutral stimulus (**conditioned stimulus** [CS]) is presented repeatedly with an **unconditioned stimulus** (UCS) that elicits a known specific response. The pairing of the UCS with the CS eventually leads to the CS alone eliciting the same (or similar) response as the UCS.[1,6] A conditioning theory thus explains placebo effects as being conditioned responses to the originally neutral stimuli generated in the therapeutic or experimental milieu.[12]

Empirical support for the conditioning model of the placebo effect comes primarily from animal studies.[16-19] Classical conditioning was first described by Pavlov,[17] who observed that dogs that salivated when fed began to salivate in response to certain nonfood stimuli that were always evident at the time of feeding, such as the sound of attendants' footsteps or the sight of a feeding dish. Pavlov reasoned that repeated association of the food stimulus with certain nonfood stimuli caused a type of conditioning, which eventually resulted in the nonfood stimuli eliciting the same physiologic reaction as the food itself. He tested his theory by ringing a bell prior to each feeding; after several trials, the dogs salivated at the sound of the bell alone. As conditioning theory predicted, the sound of the bell had become a conditioned stimulus through its association with the unconditioned stimulus of food.[4]

The first conditioned placebo effect was reported in animals by Pavlov.[17] Dogs were given morphine in an experimental chamber and specific responses to the drug were recorded. After repeated episodes of drug administration, morphine-like effects were detected in dogs upon placement into the experimental chamber before morphine was injected. The environment of the experimental chamber (the CS) came, by association, to elicit the same response as the drug itself (the UCS), resulting in a type of conditioned placebo response.[4,17]

Since Pavlov's original studies, many other instances of conditioned placebo responses have been observed in animals. Herrnstein[16] administered scopolamine hydrobromide—a drug that disrupts learned behavior in rats in a predictable manner[16]—to laboratory rats. After the rats were conditioned by several such injections, injections of a pharmacologically inert substance (a saline solution) elicited a reaction similar to that of scopolamine. Herrnstein concluded that the injection procedure was a conditioned stimulus, and the response to the saline injection was an example of a placebo effect induced by simple Pavlovian conditioning.[16] Pihl and Altman[18] reported that after rats were injected multiple times with amphetamine, injections of a saline solution elicited increased activity, as was observed with injection of amphetamine. However, after the tranquilizer chlorpromazine was used in a second experiment, injections of a saline solution did not elicit depressed activity, leading the authors to conclude that the placebo effect in rats is dependent on unknown variables that may differ among drugs and other aspects of the stimuli in the experimental chamber.[18] In dogs, injections of morphine caused vomiting, defecation, and sleep[20]; after 8 to 10 days of daily injections, dogs that were injected with physiologic saline developed the same clinical signs. Consistent with conditioning theory, the same physical response eventually was elicited merely by arrival of the experimenter in the room. The investigators concluded that "everything surrounding the patient may act as a conditioned stimulus, provoking the same illness as the original cause."[20] After rats were given insulin injections every other day for 12 days, a placebo injection of a saline solution caused increased serum glucose concentrations as a result of the conditioned physiologic response to the insulin-induced decrease in serum glucose concentrations (stress-induced hyperglycemia was proven not to be the cause of the increased glucose concentrations).[21] After rats[21] and dogs[22] were conditioned to injections of large doses of insulin that induced clinical signs of hypoglycemia (neuromuscular twitching, decreased response to stimulation, decreased activity, convulsions, semicoma), the same signs were elicited by an injection of a saline solution. The conditioning of behavioral effects of insulin is a reliable phenomenon in animals.[21] Experimentally and clinically, one of the most recognizable of conditioned responses in human and, to a lesser degree, animal patients is anticipatory emesis associated with cancer chemotherapy.[3]

Further support for the conditioning model of placebo in animals has been revealed by studies involving immunologic responses—immune responses may be suppressed or enhanced by classical conditioning.[20,23,24] In guinea pigs, scratching the skin combined with intraperitoneal injection of bacteria eventually caused immune stimulation (as measured by leukocyte proliferation in the peritoneal cavity and greater survival rate after antigenic challenge) upon skin scratching alone.[20] Guinea pigs that received a neutral stimulus (an odor) and an immunologic challenge that caused increased plasma histamine concentration had increased plasma histamine concentration of similar magnitude when later exposed to the odor alone.[25] Ader and Cohen[26,27] demonstrated that the immune system can be conditionally trained to suppress humoral and cell-mediated immune responses. In rats, pairing the neutral stimulus of a sweet taste (saccharin) with the immunosuppressive drug cyclophosphamide resulted in an immunosuppressive response (as measured by attenuation of hemagglutinating antibody titers in response to injection of sheep erythrocyte antigen) to saccharin alone.[26,27] Using the same technique, a conditioned placebo effect was revealed during disease by use of mice genetically predisposed to the autoimmune disease **systemic lupus erythematosus** (SLE).[27] Development of SLE, as measured by age of

onset, proteinuria, and mortality, was dramatically delayed by conditioned immunosuppression, compared with nonconditioned animals, thus offering definitive evidence that a pharmacologically inactive conditioned stimulus—a placebo treatment—can exert a substantial and positive therapeutic influence on the course and outcome of a disease state in animals.[27]

Research on the effects of narcotic drugs provides additional supportive evidence for the conditioning model in animals. In morphine-dependent rats[28] and monkeys[29] that have formed conditioned associations between neutral stimuli and narcotic withdrawal, the conditioned stimuli will eventually elicit the physiologic disturbances characteristic of narcotic withdrawal. If the animals are conditioned to associate a neutral stimulus with morphine substitution, the conditioned stimulus can elicit blockade of morphine withdrawal.[30] In 1 study, a neutral stimulus (the sound of a bell) was paired with morphine injections, after which the sound of the bell alone prevented withdrawal hypothermia, an effect typically accomplished by morphine.[30] Additional conditioning effects have been demonstrated by other investigators.[14,19,31] More recently, results of several studies have revealed that the placebo response can be conditioned in humans.[12,32,33]

The most comprehensive explanation of the conditioned placebo model has been proposed by Wickramasekera.[4,34] In his view, all neutral cues (places, persons, things, procedures, and rituals) surrounding the specific medical therapy may be classically conditioned by association with previously experienced ameliorative effects that have occurred in these environmental settings.[4] The UCS (the specific, active medical intervention) reduces symptoms or disease processes (the **unconditioned response** [UCR]); conditioning takes place through the repeated pairing of the UCS and neutral stimuli (CS), ultimately resulting in a physiologic response to the CS even without the active treatment component.[33] Stimuli that are similar, but not identical, to the original CS may, through generalization, come to evoke the conditioned response.[4] To the extent that neutral stimuli come to represent relief of distress, the patient's response is likely to be favorable.[14]

Experimental data in animals and humans support the notion of a conditioning model as a basis of the placebo response.[12] The conditioning model is based on learning; therefore, the conditioned placebo response will be dependent on the individual's medical history involving learned associations between neutral stimuli and an effective UCR or nonplacebo treatment.[4] Experimentally, conditioning can elicit physiologically detrimental effects as well as beneficial effects. Conditioned placebo effects may, therefore, be positive (beneficial) or negative (adverse) to the individual's health.[4] Certainly, a number of medical procedures have powerful aversive components.[4]

Expectancy—A second theory for placebo mechanisms is the cognitive model of expectancy. Placebo phenomena in humans have been described using terms such as faith, hope, and suggestion to indicate central concepts.[16,35] These factors are now conceptualized collectively as a cognitive expectancy or belief that the treatment will be effective.[4,36-38] A fundamental assumption of this model is that the effected change was causally associated with the patient's specific expectation of improvement.[4,36-38] The expectancy model in humans also appears to involve the cognitive capacity for symbolism—the ability to form and react to symbols that have come to represent certain health-modifying changes.[16]

In principle, the expectancy and conditioning models differ in their mechanisms; however, extensive overlap exists between the 2 models, because learning through personal experience is one of the major ways expectancies are formed.[4] Expectancies in humans can be formed without personal experience (which is required for a conditioned placebo response), through such methods as observational learning, acquiring information verbally or from other sources, persuasion, and other symbolic processes.[4] However, results of experimental trials in humans indicate that when conditioning and verbal expectancy are important mediators of the placebo response, conditioning is the more powerful mediator.[32] Furthermore, conditioning is not simply more potent than expectancy but, in fact, appears to be one of the mechanisms by which expectancies exert their effect.[4] Therefore, although it is clear that expectancies can be formed symbolically, conditioning over multiple trials appears to be the most effective way to form expectancies in humans.[4]

Expectancies are acquired by conditioning and other cognitive mechanisms, but this does not explain how they exert their effect. The precise mechanism by which expectancies bring about physiologic changes is not known. One of the proposed mechanisms in humans involves cognitive and emotional states of controllability, helplessness, and coping.[4] In various animals, including humans, a state of learned helplessness results when individuals do not have control over their environment—specifically, when experiencing aversive events that do not respond to efforts made at relief.[39,40] Animal experiments using escapable and inescapable electric shock, in which animals either would or would not have the control to escape from or turn off the shock, consistently reveal that the controllability or predictability of environmental stressors is the critical factor for emotional well-being and the modulation of health processes. Lack of perceived control over a stressor is related to development of many physiologic and pathologic changes in animals,[36,41] including suppressed natural killer cell activity[4] and T cell responsiveness to mitogens,[42] decreased tumor rejection, earlier tumor appearance, greater tumor size, decreased survival from tumors,[43,44] and gastric ulcers.[40] Conversely, control and predictability permit an animal to cope with stressors and are protective against adverse somatic effects associated with a variety of forms of stress.[39,40] Discomforts associated with illnesses are often experienced as uncontrollable aversive events.[4] Expectancy of relief from discomforts of disease states may provide a sense of control and hope (hope is defined as an "expectation greater than zero of achieving a goal"[45]), thereby alleviating feelings of helplessness and hopelessness, which would then

reduce the adverse influence these mental states have on somatic health. Expectancy of improvement may be experienced as a sense of hope, thereby benefiting health processes; in contrast, lack of expectancy of improvement may be experienced as hopelessness and helplessness, thereby adversely affecting health processes. In humans, interventions intended to restore control to the patient may evoke therapeutic effects that cannot readily be attributed to active treatments.[3]

To the author's knowledge, studies that specifically investigated the expectancy model of placebo in animals have not been performed. In the absence of definitive evidence for this placebo mechanism, it is reasonable to theorize the existence of the expectancy model in animals on the basis of evidence that animals possess the cognitive mechanisms suggested to be the foundation for this placebo model. Most fundamentally, a large body of research in cognitive ethology has revealed that animals have the cognitive capacity to form and act on expectations.[46] The 2 primary proposed mechanisms of the expectancy model of placebo—conditioning and learned helplessness—have been extensively documented in animals. Conditioning is the most effective way to form expectancies; learned helplessness (and associated cognitive-emotional states of control and hope) appears to be a mechanism by which expectancy exerts its effects. If animals form a learned association between treatment-related cues (eg, hospital cues, people, the way the owner behaves toward them during illness) and relief of distress,[14] this association may effect a physiologic change (as predicted by the conditioning model). In the expectancy model, having learned the association, an animal may experience a sense of hope or control for recovery, as compared with an animal that has not formed the association of neutral cues and amelioration of signs. Conversely, through conditioning, expectancy could exert a negative influence. If a learned association is formed between treatment-related cues and aversive feelings, then exposure to such cues may conceivably result in the experience of learned helplessness and hopelessness. In animals, learned aversion to foods—for example, food offered immediately before or after the administration of a drug or treatment (methotrexate, doxorubicin, erythromycin) known to cause nausea or emesis, or food force-fed to an animal during an illness—appears to involve an association of a particular taste with the sensation of nausea and a recurrence of the unpleasant sensation upon exposure to the taste stimulus.[47]

If expectancy operates through hope and control, combined with the fact that helplessness is associated with adverse effects on somatic health,[39-41] it is reasonable to surmise that an increase and decrease of control would be associated with an increase and decrease in health, respectively. As a pharmacologically inactive component of the medical intervention, such induced changes represent placebo effects.

Endogenous opiates—A third theory that has received mixed support is that placebo effects may be mediated by opioid neuropeptides.[1,4] Endogenous opiates may play a role in the placebo response in human pain, but reports have been inconsistent and often contradictory. Results of certain studies indicate that the narcotic antagonist naloxone diminishes or blocks placebo responses in the treatment of postoperative dental pain in humans,[1,48] whereas results of other studies failed to identify any effect.[49] Results of another study that used experimental ischemic pain (induced by tourniquet) indicated that naloxone diminished, but did not completely block, placebo analgesia[50]; a subsequent study using similar procedures did not reveal any effect for naloxone.[51]

All studies supporting the opiate model of placebo effect have been performed in humans and have been limited to the placebo effect associated with pain. These limitations, combined with the varied results, attest to the fact that the role of neuropeptides in mediating placebo effects is far from understood. The complexity of placebo mechanisms has led researchers to postulate that conditioning and opiate theories may both be valid, and conditioning may operate, in part, by the release of endogenous opiates as a conditioned response.[4]

Because neuropeptide communication mechanisms have been extensively demonstrated in animals,[52] the neurophysiologic foundation for opioid-mediated placebo mechanisms appears to exist in animal species. Neuropeptides comprise a system of communication between many body systems and regulate emotional mental states[52]; accordingly, this model provides a plausible mechanism for communication between mental and physical components of the body—a fundamental component of placebo processes. Because studies in animals are lacking, the role of neuropeptides (specifically, endogenous opioids) in placebo phenomena in animals is unknown and deserves investigation. It is premature to extrapolate results of the few human studies to animals, but there appears to be important potential for opioid-mediated placebo effects in veterinary patients.

Effect of human contact—A theoretical mechanism for placebo action in animals derives from a body of research demonstrating the effect of human contact on animal health. Numerous studies in animals have documented physiologic and health effects resulting from visual and tactile contact from a human. In dogs[53] and horses,[54] petting by a human is associated with substantial decreases in heart rate. Human contact elicits major changes in blood pressure, aortic blood flow, and coronary blood flow in dogs.[55] When electric shocks are administered to dogs that are simultaneously petted by a human, increase in heart rate is significantly reduced, compared with that detected when dogs are shocked without petting.[56] In farm animals, increased productivity is observed in dairy cattle handled gently,[57] and increased reproductive efficiency in sows is associated with the presence of humans.[58] In rats undergoing thyroidectomy-parathyroidectomy, mortality rate was 13% in a group petted and handled gently by a human each day since infancy, as compared with 79% in a group not handled and petted.[59] In rabbits fed a cholesterol-rich diet, those held and petted

several times a day during the trial developed arterial lesions < 50% as severe as those of control rabbits.[60]

These findings indicate that human contact appears to exert, by unknown mechanisms, a meaningful influence on the health of animals. Some researchers believe that the effect may be mediated through reduction of stress,[b] but results of many studies indicate that human contact increases stress in animals,[61,62] suggesting that the effects of human contact are not likely attributable solely to stress-mediated factors. Because human-animal contact is an integral part of veterinary medicine, effects of such contact may play a prominent role in treatment of disease. As a placebo mechanism, this effect would be a pharmacologically inactive component of the treatment.

Other mechanisms of the placebo effect—Additional mechanisms may be responsible for some placebo activity. A large body of research in animals[13,63] and humans[64,65] has revealed that stress is associated with a wide array of adverse health effects. For example, the stress of unpleasant emotional states causes immunosuppression[66,67] and enhanced tumor growth[62] in animals. If the inactive component of the medical intervention, the placebo, acts in whole or in part by alleviating the emotional stress associated with the disease state, then the animal may experience health benefits not attributable to the active component of therapy.[68] Mice maximally protected from chronic anxiety and other environmental stressors had significantly lower incidence of mammary tumors.[61] Social affiliation can mitigate the adverse immunologic consequences of social stressors in nonhuman primates.[69,70] It is plausible that by reducing anxiety and other distressing emotions, placebos could influence countless diseases, including some that we do not usually think of as subject to psychological influence.[68] However, stress reduction has limited explanatory value for the diversity of placebo actions, because such a mechanism would, by definition, only be effective in states in which stress is present and actively influencing the health status of the patient.

Modulating Influences on Placebo Effects

There is some anecdotal evidence to suggest that certain factors may modulate the expression and magnitude of the placebo effect. Straw[71] reported that in pets recovering from cancer, mental attitude of the owner had an effect. He claimed that "if the owner, veterinarian or both believe the pet will die of its cancer, they are right and the pet cannot be saved. The dedicated owner with realistic but optimistic expectations often has a dog or cat that experiences a long durable remission or cure."[71] This may simply reflect the fact that optimistic owners, as a result of that optimism, are more likely to diligently pursue and persevere with treatment. Alternately, because animals perceive and respond to emotional states of humans,[72] there may be a conveyance of optimism and hopeful expectations to the animal; the animal's mental states would thereby contribute to a somatic response consistent with expectancy theory of the placebo effect. The concept of attitude closely resembles an important variable in the magnitude of the placebo response in people.[5] Research in human patients has revealed that there is a significant correlation between the patient's attitude toward the physician and clinical improvement. Certain factors in the doctor-patient relationship augment placebo effects, including the patient's perception of the physician as empathic and likable. The authors of one study conclude that "physicians who are sensitive to these factors, who like their patients, respond positively to them, and use this factor, knowingly or unknowingly, may thereby contribute to a positive therapeutic outcome."[5] To the extent that animals form such perceptions (eg, likeability, empathy) of veterinary clinicians, it is reasonable to posit a similar influence of placebo effects in animal health care.

Veterinary Studies

Identifying placebo effects in veterinary medical studies is problematic. To the author's knowledge, studies specifically examining the placebo effect in therapeutic trials have not been reported. Placebo data for treatment trials is available only for control group results in studies investigating specific treatments. Most importantly, in trials in which placebo is selected as the control method, untreated groups that serve as second controls to distinguish placebo effects from other causes of disease resolution are not used. Even if a beneficial response is detected in the placebo group, such improvement cannot be conclusively attributed to the placebo, because nontreated individuals are not included in the study. Accordingly, specific placebo data in studies of therapeutic effects is sparse.

The most substantial placebo effect reported recently is a study of the effects of carprofen on dogs with osteoarthritis.[73] A double-blind study (neither the investigators nor the pet owners knew which drug was being administered) was conducted using dogs with lameness and radiographically confirmed osteoarthritis in a single limb. Dogs were randomly assigned to a carprofen or placebo group; placebo tablets were physically identical to carprofen tablets. Response to drug and placebo was assessed by subjective and objective criteria. Objective evaluation included force plate examination, in which ground reaction forces were recorded as dogs were trotted at a consistent velocity across a force plate. Fifty-six percent (19/34) of dogs treated with placebo had a positive response as assessed by objective measurements; interestingly, this was a greater response than reported by subjective assessment (38% reported by dog owners and 26% reported by veterinarians).[73]

Assessing the Placebo Effect

In disease states, resolution or amelioration of clinical signs potentially has different causes. To accurately assess placebo activity in any species, the effect of placebo must be distinguished from other causes of disease resolution. Four general reasons for clinical improvement in a patient's condition have been proposed[1]: natural resolution, regression to the mean, specific effects of the treatment, and nonspecific effects of treatment (placebo effect) attributable to factors other than specific active components. Regression to the

mean is a statistical concept important for its resemblance to a placebo effect.[1] Over time, measurements of most variables in biological systems fluctuate as a sine wave around a mean. Therefore, measurements of such variables at different times will likely differ and may appear as an improvement (or worsening) of the patient's condition, often mistaken for a placebo response. In controlled studies of adequate sample size and randomization, it is presumed that this variability around the mean will be the same in the placebo group as in the active treatment group, so that differences between the 2 groups relative to regression to the mean will cancel out.[1]

An additional factor that may resemble placebo effects is investigator bias. Even in blinded studies, expectations of a response may influence subjective interpretation of experimental results and erroneously attribute a response to either the placebo or treatment.

The Placebo Effect in Clinical Veterinary Medicine

The importance of the placebo effect in clinical veterinary medicine parallels its importance in human medicine. A host of nonspecific factors influence outcomes of treatments and disease processes, and mental and emotional states in animals have a large influence on somatic health processes.[13,62,63,67] A better understanding of the placebo effect would increase our understanding of psychological and psychophysiologic factors associated with medical treatment[4] and help to explain differences in responses to identical treatments among patients.[6] An understanding of the placebo effect would help explain treatment failures (through negative placebo effects) and provide suggestions to minimize such adverse effects. If the mechanisms of positive placebo effects were understood, these effects could be accentuated to augment the effects of standard therapeutic techniques.

The classical conditioning and expectancy models of placebo may have several important implications at a clinical level.[4] For placebo effects attributable to conditioning, a placebo-conditioning history is formed by every event that involves a treatment.[12] Such experiences become a determinant of the patient's future responses to placebo. Veterinary clinicians know that it is common for a patient with vomiting to cease vomiting immediately upon entry into the hospital. Although natural resolution undoubtedly accounts for this phenomenon in some instances, its frequent occurrence suggests a contribution of the placebo effect. Potential clinical applications of conditioned placebo effects are diverse. As one example, conditioned immunostimulation[20] suggests the possibility of eliciting an immunologic response (and hence greater protection against disease) by exposing a vaccinated animal to cues (CS) that have become associated with prior vaccinations, without administering an active vaccine. Conversely, conditioned immunosuppression[27] offers potentially innovative placebo-enhanced methods of fighting immune-mediated diseases. Importantly, some conditioned placebo effects will be negative[12] and are as clinically important as positive effects; in drug trials, vomiting and diarrhea are examples of effects reported in placebo-treated control subjects. In clinical practice, a thorough history might reveal whether patients are likely to respond positively or negatively to placebo effects associated with conventional treatments (eg, the hospital environment), with the goal of augmenting standard medical therapy.[74]

Alternative and holistic medicine have recently gained a strong following in human and veterinary medicine. It is feasible that effects of megavitamins, organic foods, stress reduction, holistic medicine, and acupuncture may be partially attributable to the placebo effect[5,74,75]; for example, the effects of homeopathy and placebo on symptoms of disease in humans are indistinguishable in many studies.[75]

Although data supporting placebo responses in animals are important, the conclusion that healing or a real therapeutic effect can be consistently induced as a conditioned response cannot yet be made.[76] Only limited studies in disease states, such as the effect of conditioned immunosuppression on mice with SLE,[27] have been performed.

New approaches to experimental design are necessary for specifically isolating and studying placebo effects. It may be appropriate to design follow-up studies to compare placebo-treated subjects with nontreated subjects when effects have been identified in a placebo-treated control group in a standard trial. Because it is exceedingly difficult to eliminate all treatment-related cues that can cause a placebo effect, innovative experimental design will be necessary.

The goal of clinical application of placebo effects in animals would not be to seek substitution of placebo treatments for standard treatments, but rather to use the placebo effects to accentuate the efficacy of such treatments. The overriding concern of placebo researchers in human medicine is how the placebo effect can be more effectively utilized as an adjunct to standard medical therapy.[74] As further research reveals the specific mechanisms of the placebo response, placebo effects can be accentuated and attenuated in laboratory studies, ultimately making it possible to manipulate the specific effects in clinical studies.[34] Such psychological technology can increase the reliability of obtaining a positive clinical outcome when other active treatments are used in clinical practice.[34]

[a]Shavit Y, Ryan SM, Lewis JW, et al. Inescapable but not escapable stress alters immune function (abstr). *Physiologist* 1983;26:A-64.

[b]Nerem RM, Georgia Institute of Technology, Atlanta, Ga: Personal communication, 1998.

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