Pavlovian Conditioning and Multiple Chemical Sensitivity

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Pavlovian conditioning processes may contribute to some symptoms of multiple chemical sensitivity (MCS). This review summarizes the potential relevance of the literature on conditional taste and olfactory aversions, conditional sensitization, and conditional immunomodulation to understanding MCS. A conditioning-based perspective on MCS suggests novel research and treatment strategies. — Environ Health Perspect 105(Suppl 2):521–526 (1997)

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Introduction

Multiple chemical sensitivity (MCS) is a complex and poorly understood disorder. Patients present a variety of symptoms. Sometimes precipitating events are identified, and sometimes the symptoms seem to appear without clearly defined causes. It is unlikely that any one mechanism will account for all the various manifestations of MCS.

Among the many disciplines that may contribute to our understanding of MCS is Pavlovian conditioning. Pavlovian conditioning, also termed classical or respondent conditioning, is defined by a set of operations in which a neutral conditional stimulus (CS) is paired with a biologically significant unconditional stimulus (UCS). At the start of conditioning, the UCS reflexively (unconditionally) elicits some response, termed the unconditional response (UCR). As a result of CS–UCS pairings, the CS becomes associated with the UCS. The acquisition of this association is revealed by the emergence of a new response to the previously neutral CS. Because this new response is conditional on CS–UCS pairings, it is called the conditional response (CR).

Once established, the CR may be elicited by stimuli other than the CS. Such conditional responding to novel stimuli is termed generalization. Typically, the greater the similarity between the novel assessment stimulus and the CS used in acquisition, the greater the strength of the generalized CR. The CR acquired following CS–UCS pairings may be attenuated by repeated presentations of the CS without the UCS; this procedure is called extinction.

Several phenomena studied by conditioning researchers may be relevant to MCS. This review concentrates on gustatory and olfactory aversion learning, conditioning analyses of sensitization, and conditional allergic reactions.

Gustatory and Olfactory Aversion Learning

There has been a considerable amount of research on developing an association between a flavor CS and malaise. If a distinctive flavor is followed by illness, many species (including humans) rapidly learn to associate the events (1). This association is evidenced by a behavioral avoidance of the flavor; i.e., following illness, alternative flavors are preferred to the illness-paired flavor. The association also is manifest by a negative affective reaction to the flavor; i.e., when exposed to the illness-paired flavor, rats display orofacial responses that indicate distaste (2) and people report that the flavor makes them ill (3). Flavor-aversion learning is especially robust. The aversion may readily be established (only a single pairing is necessary), and occurs despite a long interval (e.g., hours) between exposure to the flavor and the induction of illness (1).

The illness responsible for the aversion may result because the ingested substance actually contains a toxin (e.g., aversion for a food tainted with Salmonella), or because an experimenter administers the aversive agent (e.g., aversion for a harmless food that has been paired with administration of an emetic drug), or because the individual experienced an event that caused illness some time after exposure to the flavor (e.g., aversion to a food that was followed by the person’s contracting a stomach virus, or undergoing chemotherapy).

Flavor aversions are very sensitive indices of toxicosis. That is, an aversion for a normally palatable flavor develops even when only a very small dose of toxin is administered subsequent to ingestion. Indeed, such learned aversions may be more sensitive measures of toxicity than other more traditional assessments (4, 5).

Flavor-aversion learning exhibits the properties of other Pavlovian CRs. For example, such learning can be eliminated; following CS–UCS pairings, repeated presentation of the CS (flavor) without the UCS (illness) leads to diminution of the CR of aversion to the CS. Also, aversion learning displays stimulus generalization. That is, following aversion learning with one CS, other CSs that have never been paired with illness also elicit aversive CRs.

In addition to the large literature on flavor-aversion learning, there is a smaller literature on olfactory aversion learning. It is clear that olfactory cues like taste cues may acquire aversive properties following pairing with illness (6, 7). It is possible that some cases of MCS may be attributable to an instance of such olfactory or flavor aversion learning. That is, a chemical with distinctive taste and/or olfactory properties that most individuals find innocuous may elicit profound aversive responses in other individuals because in the past the chemical was paired with illness. Because the pairing may not be obvious (i.e., there was a long
interval between exposures to the sensory and noxious events), the individual may not have noticed the conditions that led to the adverse reaction to the previous neutral stimulus. There is ample evidence for such unconscious learning in the case of flavor-aversion learning by humans (3). Many toxic chemicals have distinctive odors and thus overexposure to these chemicals would necessarily involve the pairing of a distinctive olfactory cue with illness.

Case reports suggest that some individuals may have acquired MCS in a manner consistent with an aversion learning analysis. For example, Bolla-Wilson et al. (8) describe cases in which individuals became ill after accidental exposure to high levels of odorous toxic agents (e.g., insecticides or solvents) and thereafter reported various symptoms (headaches, nausea, pain in the extremities) in response to a variety of odors. That is, the illness-associated odor (e.g., odor of insecticide) as well as other odors (e.g., cigarette smoke, car fumes) elicited uncomfortable somatic symptoms. As described by Bolla-Wilson et al. (8), these symptoms may be explained as aversions to the odor paired with illness upon the occasion of the accidental exposure and stimulus generalization from the illness-paired odor to other odors.

**Sensitization to Irritants as a Learned Response**

There is an extensive literature on pharmacological conditioning (9,10). A variety of CSs (e.g., environment of drug administration, time of drug administration) when paired with administration of various pharmacological UCSs come to elicit pharmacological CRs. Although the characteristics of conditional drug responses depend on the nature and mechanism of the drug effect (11), for many effects of many drugs the pharmacological CR looks like the drug effect. That is, when presented with environmental cues that have previously signaled a drug, humans and other animals respond with druglike CRs.

When the usual drug is administered in the context of the usual predrug cues, the effect of the drug may be augmented by the pharmacological CR combining with the pharmacological UCR. As the association between the predrug cues and the drug effect grows stronger, this augmentation will become progressively greater. A progressively greater response to a drug over the course of successive administrations is termed sensitization, and there is considerable evidence that sensitization is, in part, attributable to conditioning (12).

For example, in the drug-experienced (and drug-sensitized) organism, administration of the drug in a context not previously associated with the drug often results in a reversal of sensitization; a small drug effect is seen that is characteristic of nonsensitized responding (10). Thus, by altering the context of drug administration, the effect of the drug is not augmented by any conditional drug response.

The effects of some irritants display sensitization. Mice (which are about as sensitive to formaldehyde as humans) are more sensitive to the aversive effects of an irritant on reexposure than they were on initial exposure (13). Such sensitization may also be seen with respect to the respiratory rate reduction effects of irritants; the effect increases over the course of repeated exposures (14). It is likely that conditioning contributes to such sensitization. That is, the effects of irritants can be elicited by environmental cues paired with the chemical, and the sensitized response in the irritant-experienced organism is attenuated by altering the context of irritant exposure.

If CRs contribute to irritant sensitization, it would be expected that the effects of irritants could be conditioned. Such a finding was reported by Alarie (15), who paired a light CS with an airborne irritant (ethanol). The respiratory rate reduction initially elicited by the irritant came to be elicited by the light. The contribution of this respiratory CR to sensitization is apparent in experiments that altered environmental cues. The results of such experiments suggest that sensitization is apparent only when animals are repeatedly exposed to formaldehyde in the environment in which the respiratory measurements were made (13,16,17). Thus, sensitization to irritants, like sensitization to a variety of drugs, probably is partially attributable to a CR elicited by cues paired with the chemical stimulation.

The systemic effects of irritants typically are signaled not only by environmental cues but also by cues inherent in the stimulation; the odor of the irritant and the early respiratory effects signal later irritant-induced illness. Such early effects as well as environmental stimuli may come to elicit CRs and sensitized responding. Moreover, small effects of novel irritants may elicit CRs because of generalization to the irritant that was initially presented at the time of distress. There is evidence that CRs trained with one respiratory irritant will generalize to a broad range of irritants (18).

As recently suggested by Wood and Colemen (13), the extreme sensitivity to irritants reported by some MCS patients may represent a conditional sensitized response. That is, these patients may have been exposed to irritants in the context of distinctive environmental cues. After some number of pairings, the environment itself may elicit a conditional irritant response, which may augment the responding produced by existing low levels of irritants. The individual would display sensitized responding to the irritant:

“If airborne concentrations of irritants are sufficiently aversive, they may act as unconditioned stimuli necessary for respondent conditioning to occur. Subsequent exposure to previously ineffective concentrations, or to other stimuli associated with chemical irritation, might result in the elicitation of conditioned responses that are unpleasant in and of themselves or have behavioral or other effects” (13).

**Conditional Allergic Reactions**

Some clinicians have suggested that MCS results from immune dysfunction caused by exposure to common foods and chemicals, although there is considerable evidence to the contrary (19,20). There are reports that some MCS patients display allergiclike symptoms in response to various stimuli not usually considered allergenic (21). There is an extensive literature on conditional immunological responses that may be relevant to such instances of MCS. Results of many studies indicate that stimuli that initially are neutral can, after pairing with an antigen, elicit allergic responses.

Sometimes the pairings resulting in antigenic CRs occur because there are distinctive stimuli naturally present at the time of presentation of the antigen. In 1896, Mackenzie noted that a patient who was allergic to roses displayed an allergic reaction when presented with an artificial rose (22). Apparently the visual features of the rose served as a CS for the antigenic stimulation provided by the flower. There have been many subsequent reports that a variety of nonantigenic stimuli that have been paired with antigens elicit allergic reactions (23).

There also have been laboratory demonstrations of conditional allergic reactions. For example, in an experiment using guinea pigs sensitized to egg albumin (EA), Ottenberg et al. (24) paired a distinctive injection environment (CS) with EA injections (UCS). They monitored signs such as rapid breathing, gasping, piloerection,
dilation of alae nasi, cyanosis, and convulsion. The authors reported that after training, animals had conditional allergy attacks. The symptoms were apparent when the subjects were merely placed in the injection environment (without EA challenge). Others have reported that asthmatic attacks unconditionally precipitated in guinea pigs by injection of EA could subsequently conditionally be elicited by injection of distilled water (25). MacQueen et al. (26) demonstrated that a protease specific to mast cells was released in response to an auditory CS that had in the past been paired with EA in rats sensitized to the protein.

The extensive literature on conditional immunomodulation has been reviewed elsewhere (23,27). Although there are some conflicting findings, it appears that a complete understanding of responsivity to allergens requires an appreciation of the contribution of learning to immunological responses. Of relevance to MCS are suggestions that the display of immunomodulatory CRs is affected by stress (28,29). For example, Peeke et al. (29) reported that animals that were stressed (handled) before conditioning showed significant CRs to a CS paired with bovine serum albumin. Animals that had not been stressed before conditioning did not exhibit the CR to the stimulus paired with the antigen. It is possible, then, that MCS patients may be particularly susceptible to conditional allergic responding because of high levels of stress at the time they are challenged with an antigen. Thus, a variety of stimuli present at the time of antigenic stimulation may conditionally elicit components of the allergic response.

In summary, it is possible that some MCS symptoms may be immunological CRs. Such CRs may be elicited by environmental stimuli present at the time of antigenic challenge. In some cases, the antigen-paired cue may consist of the sensory qualities (e.g., odor) of the antigenic stimulation. There is evidence that if the individual was stressed at the time of antigenic stimulation, the association between the CS and antigenic UCS is enhanced. Conditional immune responses, like other CRs, would be expected to display generalization. As a result, a variety of stimuli may come to elicit conditional allergic responses.

**Research Issues**

**Patient History**

Interviews with patients with MCS may reveal episodes consistent with a learning interpretation of their symptoms. For example, there may have been an occasion when exposure to an agent to which the patient is sensitive (the CS, according to this analysis) occurred some time before a particularly aversive event, thus establishing an association that is manifest as an aversion to the CS. Relevant to this issue is the apparently common finding that MCS patients rarely if ever develop their symptoms following exposure to odorless substances.

“We have never seen the development of these [MCS] episodic symptoms after significant exposures to odorless toxic substances such as lead or arsenic. Therefore, it appears that the person must be exposed to an odorous toxicant (solvents, chlordane) for conditioning to take place and for generalization to other substances to occur” (8).

Although the prominent role of odorous stimuli in MCS is consistent with a Pavlovian conditioning analysis of the disorder, it should be emphasized that there are a variety of reasons why exposure to odorless stimuli frequently is noted as a precursor to MCS (30).

Evaluation of the circumstances leading to development of MCS symptoms may reveal occasions on which distinctive environmental, olfactory, or gustatory cues preceded exposure to an irritant in a manner consistent with a conditioning analysis of sensitization. In cases where the MCS symptoms are exhibited as allergic-like reactions to stimuli not usually considered antigenic, it may be possible to determine occasions when a previously neutral stimulus was paired with an antigen. As previously established, there is evidence that the formation of an immunological CR may be especially pronounced if the individual is stressed at the time of CS-UCS pairing, and interviews with some patients may indicate a history of such stress in conjunction with accidental exposure to an allergen. Indeed, it has been suggested that MCS complaints are especially prevalent in people who have suffered traumatic experiences before reporting their symptoms (31).

Some instances of MCS may be attributable to generalization from the original CS to a variety of other CSs. Thus, a patient who may have developed a reaction to the odor of a solvent as a result of the pairing of this odor with illness may also display generalized aversions to other odors, such as car fumes or cut grass (8). Interviews with patients may indicate whether the extensive list of offensive agents results from such stimulus generalization of a CR. It is well established that generalization gradients flatten over time (32). That is, if a CR is established with a particular CS, there is relatively little generalization shortly after the conditioning experience, only the CS, or stimuli very similar to the CS, elicit CRs. The generalization gradient is said to be peaked at the value of the CS. However, more and more stimuli become capable of eliciting conditional responding as a function of the time since pairing. Thus, some days or weeks after CS-UCS pairing, even stimuli that are quite dissimilar from the training CS may elicit CRs. On the basis of a conditioning interpretation of MCS, it would be expected that the range of stimuli that elicit symptoms would increase as a function of the passage of time since the exposure that precipitated the disorder.

**Expectation Effects**

According to a conditioning interpretation, some symptoms of MCS may represent CRs in response to cues that in the past have been paired with a chemical. Thus, the reason why ordinarily innocuous levels of a chemical elicit symptoms is that, for example, the odor or taste of the substance actually elicits the aversive reactions. Speaking casually, according to this analysis, it is the expectation of the chemical rather than the pernicious effects of the chemical that is responsible for the patients’ complaints. To distinguish the effects of expectation of chemical from the direct effect of chemicals, investigators typically use the double-blind design. There have been suggestions that MCS patients be evaluated using the double-blind procedure (33). There are, however, more powerful designs to separate the effects of drug expectation from direct drug effects. One that has been especially useful in alcohol research is the balanced placebo design. The advantages of the balanced placebo design over the traditional double-blind procedure have been discussed elsewhere (34). Inasmuch as some MCS patients report that alcohol is one of the chemicals that elicit their symptoms (35), the balanced placebo design may be especially appropriate for separating the effects of chemical expectation from those of chemical effects in these patients.

Such balanced-placebo studies involve rather elaborate deception procedures and use beverages such as vodka and tonic mixtures in which the alcohol content is
difficult to detect. With MCS subjects who report being affected by very small doses of alcohol, only small doses need be used. Independent groups of such subjects are assigned to each cell of a 2 x 2 factorial design. One independent variable is the beverage the subject consumes (alcoholic vs. nonalcoholic), and the other independent variable is the subject’s expectation (belief) about the beverage consumed (i.e., whether the beverage is alcoholic or nonalcoholic). Thus, the balanced placebo design consists of four groups: a) subjects who consume alcohol and are correctly informed that they are consuming alcohol; b) subjects who consume alcohol but are deceived into believing they are drinking a nonalcoholic beverage; c) subjects who consume a nonalcoholic beverage and are correctly informed the beverage is nonalcoholic; and d) subjects who consume a nonalcoholic beverage but are deceived into believing they are drinking an alcoholic beverage. Various dependent variables such as estimation of alcohol exposure, symptom check list, performance on tests of cognitive function, and sleep performance may be used. If the MCS symptoms simply are elicited by alcohol, subjects in groups a and b should report symptoms (of equivalent severity), and subjects in groups c and d should not be affected. On the other hand, if the MCS symptoms are due entirely to the expectation of alcohol rather than to the effects of the drug, subjects in groups a and d should report symptoms and subjects in the other groups should not be affected. Other patterns of results would allow estimates of the relative contributions of alcohol expectancy and actual alcohol effect to MCS symptomatology.

The balanced placebo design can also be used with chemicals other than alcohol that patients report as eliciting symptoms (e.g., caffeine, chlorine in drinking water). Although the balanced placebo design is a powerful technique for distinguishing expectation effects from direct chemical effects, it does pose ethical problems because of the deception inherent in the administration of the study. These ethical problems, and ways of dealing with them, are addressed in discussions of the design (34).

Individual Differences

There are individual differences in the rates of formation of pharmacological CRs (36). Even within a highly inbred strain of rats, there are substantial individual differences in the magnitudes of taste aversion learning (37). If some cases of MCS are interpretable as instances of conditioning, it is possible that these patients are particularly susceptible to some types of conditioning. Consider the patient whose symptoms are consistent with a conditional aversion interpretation of MCS. Does this patient learn aversions especially readily? Although there are obvious ethical problems in evaluating the susceptibility of an individual to develop an aversion to a flavor paired with illness, there are procedures that may be applicable. Rotation-induced discomfort is effective in inducing an aversion for a novel flavor that precedes rotation (38), and the procedure has been used with humans (39).

Many patients receiving chemotherapy report taste aversions that are attributable to associations between the taste of food eaten before chemotherapy and the emetic effects of the chemotherapy (40–42). Those MCS patients who undergo a course of chemotherapy for cancer may provide information about the contribution of gustatory aversion learning to MCS. Are these individuals especially likely to display taste aversions as an effect of chemotherapy?

Alternatively, it is possible that MCS patients have unusually low sensory detection thresholds. They may be able to detect certain odors at very low concentration levels and thus form associations to lower concentrations of olfactory CSs than most of the population. Although there is evidence that patients with apparent MCS do not differ from controls with respect to odor detection thresholds for some chemicals (phenyl ethyl alcohol and methyl ethyl ketone), the possibility of olfactory hypersensitivity in these patients warrants further research (43).

Treatment

Once CRs are established, they can be eliminated by extinction (repeated presentation of the CS in the absence of the UCS) and counterconditioning (pairing the CS with another, nonaversive UCS). As applied to human symptoms believed to result from classical conditioning (e.g., some phobias), the treatment strategy employing these procedures is termed systematic desensitization. There are some reports that this treatment strategy is effective with some MCS patients (8,44–46). It would be of interest to evaluate systematically the efficacy of systematic desensitization as a treatment for MCS disorders.

Conclusions

This paper has summarized the potential of Pavlovian conditioning to aid in understanding some instances of MCS. It should be noted that there are learning paradigms other than Pavlovian conditioning that may contribute to our understanding of MCS. Whereas Pavlovian conditioning is concerned with an association between two events (the CS and UCS), instrumental (operant) conditioning focuses on the association between a response and a reinforcer. Instrumental conditioning can also be used in the study of MCS. For example, instrumental conditioning has been used to evaluate the aversive effects of irritants. In one recent experiment, an instrumental conditioning procedure was used that provides an elegant animal model for investigating the aversive properties of formaldehyde (13).

Many disciplines may contribute to our understanding of MCS. Certainly learning in general or Pavlovian conditioning in particular do not provide explanations for all the bewildering array of symptoms presented by MCS patients. Nevertheless, as summarized here, there are several issues inspired by a conditioning-based perspective on MCS that provide opportunities for research about both the etiology of some cases of MCS and effective treatment strategies.

Finally, some clinicians do not favor conditioning analyses of MCS (44,47). They suggest that this approach minimizes the physical basis of the MCS patients’ symptoms and treats them merely as psychological complaints. Such a view, however, is a misconception of conditioning. Individuals who salivate when a lemon is being sliced, experience hunger pangs when anticipating a meal, or avoid a food that in the past preceded gastrointestinal illness, are displaying CRs. The tendency to associate events is as physiological as any other biological process. It is not surprising that CRs can have profound effects such as those seen in some instances of MCS. Results of previous research indicate that CRs importantly contribute to physiological functioning and the maintenance of homeostasis (48). They also can modulate the lethal effects of several drugs (49–51) and alter the course of autoimmune diseases (52). Given the ready applicability of the Pavlovian conditioning paradigm to many instances of MCS, it is possible, as suggested by Bolla-Wilson et al. (8), that “the causal mechanism for prolonged physical symptoms and sensitivity to common environmental substances can best be conceptualized in a classical conditioning model.”
REFERENCES

1. Braveman NS, Bronsten P, eds. Experimental Assessments and Clinical Applications of Conditioned Food Aversions. New York: New York Academy of Sciences, 1985.
2. Spector AC, Brelin P, Grill HJ. Taste reactivity as a dependent measure in the rapid formation of conditioned taste aversion: a tool for the neural analysis of taste–visceral associations. Behav Neurosci 102:942–952 (1988).
3. Logue AW. Conditioned food aversion learning in humans. In: Experimental Assessments and Clinical Applications of Conditioned Food Aversions (Braveman NS, Bronsten P, eds). New York: New York Academy of Sciences, 1985:316–329.
4. Parker LA, Hutchison S, Riley AL. Conditioned flavor aversions: a toxicity test of the anticholinesterase agent, phystostigmine. Neurobehav Toxicol Teratol 4:93–98 (1982).
5. Riley AL, Tuck DL. Conditioned taste aversions: a behavioral index of toxicity. In: Experimental Assessments and Clinical Applications of Conditioned Food Aversions. Vol 443 (Braveman NS, Bronsten P, eds). New York: Annals of the New York Academy of Sciences, 1985:272–292.
6. Alleva E. Odor-aversion learning and retention span in neonatal mouse pups. Behav Neural Biol 46:348–357 (1986).
7. Darling FMC, Slotten BM. Odor-cued taste avoidance: a simple and efficient method for assessing olfactory detection, discrimination, and memory in the rat. Physiol Behav 53:817–822 (1994).
8. Bolla-Wilson K, Wilson RJ, Bleecker ML. Conditioning of physical symptoms after neurotoxic exposure. J Occup Med 30:684–686 (1988).
9. Cunningham C L. Pavlovian drug conditioning. In: Methods in Behavioral Pharmacology (van Heeren F, ed). Amsterdam/Elsevier, 1993:349–378.
10. Siegel S. Feedforward processes in drug tolerance. In: Perspectives in Cognitive Neuroscience (Lister R G, Weingartner HJ, eds). New York: Oxford, 1991:405–416.
11. Siegel S. Classical conditioning and opiate tolerance and withdrawal. In: Psychotropic Drugs of Abuse (Balfour DJK, ed). New York: Pergamon, 1990:59–85.
12. Stewart J. Conditioned stimulus control of the expression of sensitization of the behavioral activating effects of opiate and stimulant drugs. In: Learning and Memory: Behavioral and Biological Substrates (Gormezano I, Wasserman EA, eds). Hillsdale, NJ: Erlbaum, 1992:129–151.
13. Wood RJ, Coleman JB. Behavioral evaluation of the irritant properties of formaldehyde. Toxicol Appl Pharmacol 130:67–72 (1995).
14. Consumer Product Safety Commission. Ban of urea-formaldehyde foam insulation. Fed Reg 47:14366–14419 (1982).
15. Alarie Y. Irritating properties of airborne materials to the upper respiratory tract. Arch Environ Health 13:433–439 (1966).
16. Chang JC, Steinheugen WH, Barlow CS. Effect of single or repeated formaldehyde exposure on minute volume of B6C3F1 mice and F-344 rats. Toxicol Appl Pharmacol 61:451–459 (1981).
17. Kane LE, Alarie Y. Sensory irritation to formaldehyde and acrolein during single and repeated exposures in mice. Am Ind Hyg Assoc J 38:505–522 (1977).
18. Allen WF. Olfactory and trigeminal conditioned reflexes in dogs. Am J Physiol 185:532–540 (1957).
19. Terr AI. Clinical ecology: American College of Physicians. Ann Intern Med 111:168–178 (1989).
20. Terr AI. Environmental illness. A clinical review of 50 cases. Arch Int Med 146:145–149 (1986).
21. McGovern JJ, Lazaroni JA, Hicks MF, Adler JC, Cleary P. Food and chemical sensitivity: clinical and immunologic correlates. Arch Otolaryngol Head Neck Surg 109:292–297 (1983).
22. MacKenzie JN. The production of the so-called "rose" cold by means of an artificial rose. Am J Med Sci 91:45–47 (1896).
23. Ader R, Cohen N. The influence of conditioning on immune responses. In: Psychoneuroimmunology, 2nd ed (Ader R, Felten DL, Cohen N, eds). San Diego: Academic Press, 1991:611–646.
24. Ottenberg P, Stein M, Lewis J, Hamilton C. Learned asthma in the guinea pig. Psychosom Med 20:395–400 (1958).
25. Justesen DR, Braun EW, Garrison RB, Pendleton RB. Pharmacological differentiation of allergic and classically conditioned asthma in the guinea pig. Science 170:864–866 (1970).
26. MacQueen G, Marshall J, Perdue M, Siegel S, Bienenstock J. Pavlovian conditioning of rat mucosal mast cells to secrete rat mast cell protease II. Science 243:83–85 (1989).
27. Ader R, Felten D, Cohen N. Interactions between the brain and the immune system. Annu Rev Pharmacol Toxicol 30:561–602 (1990).
28. Gorczynski RM, Macrae S, Kennedy M. Factors involved in the classical conditioning of antibody responses in mice. In: Breakdown in Human Adaptation to “Stress”: Towards a Multidisciplinary Approach (Ballieux RE, Fielding JF, L’Abbate A, eds). Huningham, MA: Martinus Nijhoff, 1984:704–712.
29. Peeke HVS, Dark K, Ellman G, McMurty C, Salji M. Prior stress and behaviorally conditioned histamine release. Physiol Behav 39:89–93 (1987).
30. Nielsen GD. Mechanisms of activation of the sensory irritant receptor by airborne chemicals. Crit Rev Toxicol 21:183–208 (1991).
31. Pennebaker JW. Psychological bases of symptom reporting: perceptual and emotional aspects of chemical sensitivity. Toxicol Ind Health 10:497–511 (1994).
32. Riccio DC, Ackil J, Burch-Vernon A. Forgetting of stimulus attributes: methodological implications for assessing associative phenomena. Psychol Bull 112:433–455 (1992).
33. Neutra RR. Some preliminary thoughts on the potential contribution of epidemiology to the question of multiple chemical sensitivity. Pub Health Rev 22:271–28 (1994).
34. Marlatt GA, Rohsenow DJ. Cognitive processes in alcohol use: expectancy and the balanced placebo design. In: Advances in Substance Abuse: Behavioral and Biological Research (Mello NK, ed). Greenwich, CT: JAI Press, 1982:159–199.
35. Bell IR, Peterson JM, Schwartz G. Medical histories and psychological profiles of middle-aged women with and without self-reported illness from environmental chemicals. J Clin Psychiatry 56:151–160 (1995).
36. Irwin S, Armstrong PM. Conditioned locomotor response with drug as the unconditioned stimulus: individual differences. Neuropsychopharmacology 2:151–157 (1961).
37. Turetten S, Miles C, Parker L, Siegel S. Individual differences in reactivity to the rewarding/aversive properties of drugs: assessment by taste and place conditioning. Pharmacol Biochem Behav 53:511–516 (1996).
38. Kinney NE, Wright JW, Herding JW. Motion-induced aversions during and after recovery from olfactory nerve section in mice. Physiol Behav 53:631–633 (1993).
39. Arwas S, Rolnick A, Lubow RE. Conditioned taste aversion in humans using motion-induced sickness as the US. Behav Res Ther 27:295–301 (1989).
40. Andrykowski MA, Orts ML. Development of learned food aversions in humans: investigation in a “natural laboratory” of cancer chemotherapy. Appetite 14:145–158 (1990).
41. Bernstein IL. Aversion conditioning in response to cancer and cancer treatment. Clin Psychol Rev 11:185–191 (1991).
42. Jacobson PB, Bovbjerg DH, Schwartz MD, Andrykowski MA, Futterman AD, Gilewski T, Norton L, Redd WH. Formation of food aversions in cancer patients receiving repeated infusions of chemotherapy. Behav Res Ther 31:739–748 (1993).
43. Dory RL. Offaction and multiple chemical sensitivity. Toxicol Ind Health 10:359–368 (1994).
44. Bolla-Wilson K, Bleecker ML. Reply to Zeim’s letter. J Occup Med 31:411 (1989).
45. Guglielmi RS, Cox DJ, Spyker DA. Behavioral treatment of phobic avoidance in multiple chemical sensitivity. J Behav Ther Exp Psychiat 25:197–209 (1994).
46. Spyker DA. Multiple chemical sensitivities—syndrome and solution. J Toxicol Clin Toxicol 33:95–99 (1995).
47. Zeim G. Physical symptoms after neurotoxic exposure. J Occup Med 31:410–411 (1989).
48. Dworkin BR. Learning and Physiological Regulation. Chicago: University of Chicago Press, 1993.
49. Melchior CL. Conditioned tolerance provides protection against ethanol lethality. Pharmacol Biochem Behav 37:205–206 (1990).
50. Siegel S, Hinson, RE, Krank MD, McCully J. Heroin "overdose" death: the contribution of drug-associated environmental cues. Science 216:436–437 (1982).
51. Vila CJ. Death by pentobarbital overdose mediated by Pavlovian conditioning. Pharmacol Biochem Behav 32:365–366 (1989).
52. Ader R, Cohen H. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. Science 215:1534–1536 (1982).