Human Drug Drug Discrimination and Multiple Chemical Sensitivity: Caffeine Exposure as an Experimental Model

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Multiple chemical sensitivity is a controversial diagnosis. Rigorous, controlled, laboratory-based research can reduce this controversy and lead to potential clinical confirmatory tests. The literature on human caffeine discrimination provides a rigorous methodology that can address reports that patients who suffer multiple chemical sensitivity (MCS) are sensitive to usually well-tolerated chemical doses; the studies require patients to discriminate caffeine from placebo under double-blind conditions. Several issues relevant to the conduct of caffeine discrimination studies using MCS patients as subjects are addressed: these issues include study design, determination of safe and tolerable training doses, and discrimination training. Such research will benefit patients and clinicians dealing with a diagnosis of MCS. — Environ Health Perspect 105(Suppl 2):509–513 (1997)

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Introduction

A diagnosis of multiple chemical sensitivity (MCS) is controversial, in part because the term means different things to different people. For the MCS patient seeking treatment, the term can mean an adverse and often medically unrecognized condition marked by a variety of symptoms (e.g., lethargy, fatigue, memory difficulties, shortness of breath) that can arise from exposure to previously tolerated chemical stimuli (e.g., car exhaust, perfume, alcohol or caffeine) (1). For the clinician attempting to treat the MCS patient, the term can mean a disorder with no accepted diagnostic criteria or confirmatory laboratory markers and few treatments. To the researcher interested in studying MCS, the term represents the difficult empirical problem of studying a condition that may require exposure to potentially aversive or toxic stimuli. The purpose of this report is to suggest a powerful empirical method that can be used to study MCS in humans: drug discrimination using caffeine as a discriminative stimulus. Before describing this methodology and its potential applications, we first provide a brief overview of MCS. We then discuss the variability in the range of caffeine doses that can be detected across subjects and the types of subjective effects that are reported by normal human volunteers who participate in caffeine discrimination studies. We also discuss how MCS patients may represent a special population that is exquisitely sensitive to caffeine’s effects. Finally, we suggest issues that researchers should consider when planning research in caffeine discrimination involving volunteer MCS patients. Such research should positively impact MCS patients and clinicians as they deal with a debilitating but ill-defined disorder.

What is Multiple Chemical Sensitivity?

While many definitions exist (2,3), the term MCS is most often applied to an acquired non-IgE-mediated reaction in one or more organ systems to normally non-toxic chemical stimuli. MCS patients often report a wide range of symptoms that are elicited by various stimuli. For example, in a recent study of 112 MCS patients, the four most frequently reported symptoms were "tired or lethargic," "fatigue > 6 months," "memory difficulties," and "difficulty concentrating" (1,2). While many respondents reported that their symptoms could be elicited by airborne stimuli (diesel or gas engine exhaust, perfume, etc.), a substantial proportion of respondents also implicated ingested items as symptom elicitors, including alcohol, chlorinated water, and cane sugar. Some 30% or more of respondents indicated that caffeine-containing items (chocolate, cola, coffee, or tea) elicited their symptoms (1). Such evidence might imply that MCS patients, especially those who report sensitivity to dietary sources of caffeine, may represent a special population exquisitely sensitive to low-dose caffeine.

In part because MCS patients report that so many inhaled and ingested chemical stimuli elicit symptoms, and also because elicited symptoms vary markedly across individuals, a diagnosis of MCS is controversial (1,4,5). Several professional organizations have found no current evidence to support the diagnosis of MCS or to support clinical ecology, the branch of medicine created to treat the disorder (6–9). However, many of these same organizations recognize the need for well-controlled laboratory studies of the phenomenon (7,8). The fact that many MCS patients report sensitivity to caffeine, coupled with a thriving caffeine discrimination literature, suggests that caffeine discrimination methodology may be an excellent starting point for well-controlled studies of MCS.

Caffeine Discrimination in Normal Human Volunteers

Several well-controlled studies have investigated caffeine discrimination using normal human volunteers. Typically, these studies involve intensive, within-subject presentations of placebo and active doses of caffeine over the course of many discrete trials. For example, Mumford et al. (10) reported the results of a caffeine discrimination study involving seven subjects who participated in 30 to 100 trials (1 trial per day). On each trial, subjects were asked to discriminate placebo from an active caffeine dose. As described below, this study, or others using a similar methodology, demonstrate that there is considerable individual variability in the range of doses of caffeine that
can be discriminated from placebo, and that caffeine challenge can produce either positively or negatively rated subjective effects depending upon caffeine dose. Also, people who do not use caffeine report that caffeine produces more aversive effects than people who do use caffeine regularly (11). These results are consistent with the hypothesis that some individuals (e.g., MCS patients) may be extremely sensitive to caffeine and that, for these individuals, dietary doses of caffeine may be aversive.

First, the range of caffeine doses that are reliably detected by normal volunteers varies widely across individuals (12,13). For example, Griffiths et al. (12) reported a study of seven caffeine users who abstained from all dietary caffeine, and then were trained to discriminate 100 (n = 1) or 178 (n = 6) mg caffeine from placebo. After learning the discrimination, all subjects were tested to determine the lowest caffeine dose that they could reliably discriminate from placebo. Results indicated individual differences in the threshold of caffeine discrimination, ranging from a low of 10 mg to a high of 56 mg caffeine (Figure 1). Other reports involving explicit discrimination training of low-dose caffeine indicate that about 70% of subjects can detect 56 mg or less of caffeine, and 35% of subjects can detect 18 mg or less of caffeine (14). These results clearly indicate that, in the normal human population, there is considerable variability in sensitivity to caffeine. The determinants of this variability have not been systematically studied. Factors that would probably contribute to such variability might include the extent of prior caffeine exposure and the choice of measurement technique. Nonetheless, a methodology clearly exists for measuring sensitivity to low-dose caffeine.

Second, normal volunteers report qualitative differences in caffeine’s subjective effects, depending upon dose, as follows: Low to moderate doses (20–200 mg) produce predominantly positive effects, including increased ratings of alertness, concentration, desire to talk, energy/activity, motivation to work, self-confidence, and sense of well-being. These doses also decreased ratings of “muzziness” (not clearheaded) and sleepiness. High doses (200–500 mg) produce predominately dysphoric effects, including ratings of increased anxiety, bad effects, jitteriness, nervousness, and shakiness (10,11,13,18). Thus, depending on dose taken in, caffeine can produce both positive and aversive effects in the general population.

While the type of subjective effects produced by caffeine depends upon dose, the intensity of caffeine’s subjective effects may be determined by an individual’s sensitivity to low-dose caffeine. That is, there is a strong negative correlation between an individual’s lowest detectable caffeine dose (threshold of detection) and the magnitude of subjective response to 178 mg caffeine (r = -0.91) (Figure 2) (12). Thus the lower the dose of caffeine that an individual can detect, the greater the magnitude of that individual’s response. This relationship may be particularly important to caffeine-sensitive MCS patients. That is, individuals who are able to detect extraordinarily low caffeine doses may be more likely to report that dietary doses of caffeine produce aversive effects. These results are consistent with the idea that even low doses of caffeine may be strongly aversive to some caffeine-sensitive individuals.

Finally, although a large proportion of the population chooses to consume caffeine (e.g., > 80% of adults in North America regularly consume behaviorally active doses) (15–17), some individuals for various reasons do not. Individuals who do not use caffeine may represent a subpopulation for whom dietary doses of caffeine are aversive, either as a result of an innate or acquired sensitivity to the drug. In one study designed to examine reasons for caffeine use or nonuse, Goldstein et al. (11) administered 0, 150, and 300 mg caffeine to self-reported caffeine users (n = 38) or nonusers (n = 18). Users reported positive
subjective effects after caffeine administration (e.g., increased alertness, decreased irritability) whereas nonusers reported negative subjective effects after caffeine administration (e.g., jitteriness, nervousness). Evans and Griffiths (18) reported compatible results in a laboratory-based study of 32 moderate caffeine users who abstained from dietary caffeine. In that double-blind study subjects were challenged on one day with caffeine (total dose = 600 mg) and on another day with placebo in color-coded capsules. Subjects were identified as caffeine choosers \((n = 12)\) or nonchoosers \((n = 20)\) based on their choice of placebo- or caffeine-containing color-coded capsules on a subsequent choice day. Figure 3 shows that, after receiving caffeine, nonchoosers' subjective ratings of tension/anxiety and jittery/nervous/shaky increased relative to receipt of placebo doses and relative to choosers' ratings after caffeine administration. Thus caffeine nonchoosers reported significantly greater negative effects following caffeine challenge than did caffeine choosers. Both of these studies demonstrate that, in the normal population, a given dose of caffeine can produce aversive effects in some individuals but not in others.

**Caffeine and MCS Patients**

MCS patients may represent a population with an acquired sensitivity to caffeine as well as other inhaled or ingested chemical stimuli. As such, when MCS patients are compared to normal volunteers the MCS patients could be expected to have a lower threshold of caffeine detectability and a greater likelihood of reporting negative subjective effects to low-dose caffeine. Certainly these predictions are supported by self-reports (J). If this hypothesized sensitivity to caffeine could be demonstrated using rigorous, double-blind, well controlled methodology, the syndrome of MCS would receive some of the empirical support that some professional medical organizations suggest it currently lacks.

There are many advantages to using caffeine discrimination as a model preparation to study MCS: caffeine is safe, it can be conveniently administered in a double-blind manner, and its pharmacology—at least in normal humans—is well understood. In contrast, other potential preparations that might be used to study MCS, such as airborne challenges with various chemicals, are less convenient, are often difficult to deliver in a double-blind manner due to strong olfactory/gustatory stimuli, and have less well-known and potentially less safe pharmacological profiles. The success of human drug discrimination studies using caffeine as a discriminative stimulus in normal humans \((10,12,18-20)\) suggests that this methodology might be applied successfully to studies involving MCS patients. Below we discuss issues relevant to studies that use discrimination methodology to investigate MCS in the human behavioral pharmacology laboratory.

**Studying Caffeine Sensitivity in MCS Patients**

A study of caffeine sensitivity in MCS patients could be designed to determine if self-identified caffeine-sensitive MCS patients are able to discriminate lower doses of caffeine than normal controls, and to determine if these MCS patients report aversive effects of caffeine under double-blind dosing conditions. Such a study would thus address two unresolved issues in the MCS literature: the reported sensitivity to usually well-tolerated doses of chemical stimuli and the lack of well-controlled studies demonstrating that low-dose chemical stimuli elicit the constellation of symptoms reported by MCS patients. Studies designed to address these issues must include carefully crafted instructions for subjects, may include control groups to increase the rigor of the study, and may also include procedures that allow tolerable dose exposure for all subjects. Each of these ideas is briefly discussed below.

Informed consent is an essential part of any study involving human subjects and would be particularly important when administering caffeine challenges to MCS patients, since active drug administration could result in an aversive response. All subjects must be informed prior to their participation that they will receive both placebo and active caffeine-containing capsules throughout the study. However, subjects must also be aware that they may not be informed of the contents of any given capsule. Subjects should also be informed that they must pay attention to the effects of every dose, as they may be asked to identify each dose based upon its effects.

One of the strengths of the drug discrimination paradigm is that the intensive within-subject methodology allows statistical analysis at the level of the individual. However, in studies of special populations, this within-subject methodology may be enhanced by the addition of a between-groups component to allow for cross-group comparison or to control for potential population-specific confounding variables. For example, a study of caffeine sensitivity in MCS patients would almost certainly involve a sample of MCS patients who report that dietary doses of caffeine elicit their MCS symptoms. However, such a group may be caffeine avoidant (21). Thus non-MCS patients who do not regularly use caffeine might be included to determine if caffeine avoidance influenced the observed results. Similarly, a group of MCS patients who report that they are not sensitive to caffeine might be considered, to control for the impact of MCS diagnosis.
itself. These between-groups comparisons can help to determine if MCS patients are differentially sensitive to caffeine.

A study of MCS patients may also include a comparison group of normal, moderate caffeine users who abstain from caffeine throughout the study. One of the primary advantages of using a well-accepted and frequently used methodology is the ability to compare new results to previous work. For this reason, normal, moderate caffeine users might be included in a study of MCS patients to demonstrate that the study methodology yielded results similar to those already in the literature (12,13).

Determination of a safe and tolerable training dose is a major issue in any caffeine discrimination study involving caffeine-sensitive MCS patients. High training doses may lead to quick acquisition of the discrimination, but may elicit symptoms that would be intolerable to MCS patients. In contrast, low training doses may be tolerable but may make the caffeine-placebo discrimination difficult to acquire. Thus individualizing the training dose after a brief, ascending dose, threshold-of-detection phase may be valuable. All subjects participating in the study could participate in the threshold-of-detection phase, which would involve daily administration of a single capsule containing either placebo or active caffeine. The primary goal of this phase would be to determine safe and tolerable doses of caffeine that might be used in a later discrimination phase. Ideally, the ratio of placebo to active drug trials in the threshold-of-detection phase would be high, to determine a base rate of placebo responding (i.e., false positives) and to allow for adequate washout time between active doses. Also, initial doses of active caffeine might be lower than doses to which the general population is sensitive, because one hypothesis of the study is that caffeine-sensitive MCS patients are more sensitive to caffeine than the general population. An example of a threshold-of-detection phase might involve a 4:1 placebo:active dose ratio, with the amount of active dose ranging from 1.0 to 100.0 mg caffeine. Sessions would involve administration of a single capsule, followed by subjective ratings of drug effects and attempts to identify the presence or absence of active caffeine. Once an individual has correctly detected an active dose, that correct detection should be replicated several times to reduce the possibility of a chance identification. This phase would yield only preliminary results, useful for planning safe and tolerable discrimination training. Assuming that subjects are willing to repeatedly self-administer their individually determined threshold dose, discrimination training could begin.

Discrimination training, during which subjects learn to discriminate placebo from the effects of active drug, is the heart of any drug discrimination study. During training, subjects are presented with placebo and tolerable active drug doses (determined from the threshold of detection phase) that have been previously identified by a letter code. Subjects earn money for correctly identifying (by code letter) which compound they received on each day (13). The discrimination is said to be learned when subjects correctly identify some criterion percentage (e.g., > 80% of more than 10 presentations) of presented capsules. If the discrimination is not learned, a higher active dose is used and the process is repeated. Once a discrimination at a given dose has been learned, subjects repeat the procedure using a lower active dose. In this manner, the lowest discriminable dose for each individual can be determined (10,12,13), and any potential differences in discriminable doses between groups (e.g., MCS patients vs normal controls) can be examined. Thus, drug discrimination methodology can be used to determine if MCS patients are more sensitive to caffeine than various control groups. Also, the addition of concurrent subjective measures would permit the determination of the types of responses elicited by caffeine challenge in MCS patients and would allow comparison to the caffeine-elicited responses of various control groups.

The wide variety of chemical stimuli that may elicit MCS symptoms increases the potential for extraneous variability in a laboratory study of MCS patients. Stimuli encountered during normal daily activity or in the laboratory may elicit MCS symptoms that could be mistakenly attributed to the study drug. To avoid this potential bias, drug discrimination studies of MCS patients may involve sessions that all subjects run in their own homes. Subjects would be able to pick up a supply of study forms and capsules, and conduct sessions in an environment that is relatively free of symptom-eliciting environmental stimuli. Scheduling of sessions would be subject-determined, so that no sessions would take place when an MCS patient was symptomatic; environmentally induced MCS symptoms may mask the symptoms produced by the study drug (21).

Conclusions

MCS patients and their physicians will both benefit from rigorous, well-controlled research designed to empirically address the validity of the MCS diagnosis. Caffeine discrimination studies are one example of a research program that could better characterize an ill-defined disorder. Regardless of the outcome, well-designed empirical studies of MCS can improve diagnostic and treatment techniques. Studies that fail to demonstrate the reproducibility of the disorder under rigorous laboratory conditions will suggest that symptoms might best be attributed to a cause other than toxicity of chemical stimuli. Studies that demonstrate the reproducibility of the disorder under rigorous laboratory conditions will support the MCS diagnosis, improve acceptance of the disorder within the medical community, and lead to effective treatments through continued research.

REFERENCES

1. Miller CS, Mitzel, HG. Chemical sensitivity attributed to pesticide exposure versus remodeling. Arch Environ Health 50:119–129 (1995).
2. Miller CS. White paper: chemical sensitivity: history and phenomenology. Toxicol Ind Health 10:253–276 (1994).
3. Nethercott JR, Davidoff LL, Curb WB, Abbey H. Multiple chemical sensitivities syndrome: toward a working case definition. Arch Environ Health 48:19–26 (1993).
4. Black DW. Environmental illness and misdiagnosis—a growing problem. Regul Toxicol Pharmacol 18:23–31 (1993).
5. Terr IA. Immunological issues in multiple chemical sensitivities. Regul Toxicol Pharmacol 18:54–60 (1993).
6. American Academy of Allergy and Immunology. Position statements: clinical ecology. J Allergy Clin Immunol 78:269–271 (1986).
7. American College of Physicians. Position paper: clinical ecology. Ann Intern Med 111:168–178 (1989).
8. American Medical Association. Council report: clinical ecology. J Am Med Assoc 268:3465–3467 (1992).
9. Board of the International Society of Regulatory Toxicology
and Pharmacology. Report of the ISRTP Board. Regul Toxicol Pharmacol 18:79 (1993).

10. Mumford GK, Evans SM, Kaminski BJ, Preston KL, Sannerud CA, Silverman K, Griffiths RR. Discriminative stimulus and subjective effects of theobromine and caffeine in humans. Psychopharmacology 115:1–8 (1994).

11. Goldstein A, Kaizer S, Whitby O. Psychotropic effects of caffeine in man. IV: Quantitative and qualitative differences associated with habituation to coffee. Clin Pharmacol Ther 10:489–497 (1969).

12. Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerud CA, Wolf B, Woodson PP. Low-dose caffeine discrimination in humans. J Pharmacol Exp Ther 252:970–978 (1990).

13. Silverman K, Griffiths RR. Low-dose caffeine discrimination and self-reported mood effects in normal volunteers. J Exp Anal Behav 57:91–107 (1992).

14. Griffiths RR, Mumford GK. Caffeine reinforcement, discrimination, tolerance and physical dependence in laboratory animals and humans. In: Pharmacological Aspects of Drug Dependence—Towards an Integrated Neurobehavioral Approach. Handbook of Experimental Pharmacology (Schuster CR, Gust SW, Kuhar MJ, eds). New York: Springer Verlag. 1996;315–341.

15. Gilbert RM. Caffeine as a drug of abuse. In: Research Advances in Alcohol and Drug Problems. Vol 3 (Gibbins RJ, Israel Y, Kalant H, Popham RE, Schmidt W, Smart RG, eds). New York: John Wiley & Sons, 1976:49–176.

16. Graham DM. Caffeine—its identity, dietary sources, intake and biological effects. Nutr Rev 36:97–102 (1978).

17. Hughes JR, Oliveto AH, Bickel WK, Higgins ST, Badger GJ. Caffeine self-administration and withdrawal: incidence, individual differences and interrelationships. Drug Alcohol Depend 32:239–246 (1993).

18. Evans SM, Griffiths RR. Caffeine tolerance and choice in humans. Psychopharmacology 108:51–59 (1992).

19. Oliveto AH, Hughes JR, Higgins ST, Bickel WK, Pepper SL, Shea PJ, Fenwick JW. Forced-choice versus free-choice procedures: caffeine self-administration in humans. Psychopharmacology 109:85–91 (1992).

20. Oliveto AH, Bickel WK, Hughes JR, Terry SY, Higgins ST, Badger GJ. Pharmacological specificity of the caffeine discriminative stimulus in humans: effects of theophylline, methylphenidate and buspirone. Behav Pharmacol 4:237–246 (1993).

21. Miller CS. Toxicant-induced loss of tolerance: an emerging theory of disease? Environ Health Perspect 105(Suppl 2): 445–453 (1997).