d-amphetamine, nicotine) generally do not. However, cocaine and methylphenidate have also been shown in some studies to fully substitute for caffeine. In animals trained to discriminate amphetamine or cocaine from vehicle, studies have consistently found that caffeine partially substitutes for these drugs, usually producing 50–60% drug-appropriate responding. Such partial substitution was also observed in a study in which caffeine was tested in humans trained to discriminate between *d*-amphetamine and placebo. Humans have been trained to discriminate caffeine from placebo at doses as low as 10–56 mg, but to date no generalization testing with the drugs has been performed in caffeine-trained human subjects. A variety of techniques have been used to study the subjective effects of caffeine in humans, including ratings of general stimulus effects, visual analog scales, and standardized questionnaires such as the Addiction Research Center Inventory (ARCI) and the Profile of Mood States (POMS). Significant effects of caffeine on mood have been demonstrated at doses below 100 mg. In general, doses of caffeine in the range of 100–200 mg increase scores on measures indicating stimulation and vigor, whereas doses of 300 mg or higher tend as well to produce aversive symptoms such as increased anxiety and jitteriness. The profile of mood effects produced by caffeine has both similarities and differences compared with those produced by other psychomotor stimulants. The relationship between the subjective and discriminative stimulus effects of caffeine, the effects of level of habitual caffeine use on subjective response to caffeine, and other factors responsible for individual differences in subjective response to caffeine will also be addressed.

REINFORCING EFFECTS OF CAFFEINE IN HUMANS. Roland R. Griffiths and Suzette M. Evans. The Johns Hopkins University School of Medicine and The National Institute on Drug Abuse, Baltimore, MD.

This paper reviews a series of studies that have been conducted in our laboratory which have begun to characterize the reinforcing effects of caffeine in both residential and nonresidential human volunteers. Several of the studies have demonstrated unequivocally that caffeine can function as a reinforcer: Compared to coffee or capsules without caffeine, caffeine-containing coffee and capsules maintained higher levels of self-administration and were preferred in choice tests. Caffeine-containing coffee and capsules were also rated as being better liked than coffee and capsules without caffeine. Data from some studies suggest that the reinforcing effects of caffeine can be potentiated by a history of recent caffeine exposure; however, such a history is not a necessary condition for demonstrating caffeine reinforcement. Other studies have shown that both tolerance to subjective effects and withdrawal upon termination of dosing can be produced by chronic caffeine administration. Both tolerance and physical dependence provide potential mechanisms underlying the potentiation of reinforcement by recent caffeine exposure. While caffeine reinforcement has been reliably demonstrated with subjects with histories of very heavy caffeine use, studies have also documented individual differences in susceptibility to caffeine among normal subjects. There are some data showing that caffeine choice varies inversely with prestudy levels of anxiety, suggesting that trait anxiety may be useful in identifying individuals who are particularly sensitive to the aversive effects of caffeine. Other data indicate that caffeine choosers and nonchoosers show distinctly different profiles of caffeine subjective effects: 1) choosers show "positive" subjective effects of caffeine relative to placebo; 2) nonchoosers show "negative" effects of caffeine relative to placebo and tolerance develops to some of these effects with chronic caffeine administration; and 3) choosers showed "negative" effects of placebo relative to the effects of placebo in nonchoosers. The continued investigation of behavioral and pharmacological mechanisms underlying the reinforcing effects of caffeine, the most widely used behaviorally active drug in the world, should provide valuable insights into the general nature of the drug dependence process.

PHYSICAL DEPENDENCE ON CAFFEINE. Suzette M. Evans and Roland R. Griffiths. The National Institute on Drug Abuse and The Johns Hopkins University School of Medicine, Baltimore, MD.

This paper reviews a series of studies conducted in our laboratory which have examined caffeine physical dependence as manifested by a withdrawal syndrome upon termination of chronic administration. Our first study, which was conducted in residential subjects who had histories of heavy caffeine consumption, examined caffeine withdrawal by substituting decaffeinated for caffeinated coffee for 10 or more days. A withdrawal syndrome, characterized by increases in headache and fatigue, peaked on days 1 and 2 and decreased over the next 5 to 6 days. In our second study, which was conducted in subjects with experimental histories of discriminating caffeine from placebo, withdrawal was examined by substituting placebo for caffeine-containing capsules. The study showed that the incidence of caffeine withdrawal was higher, the daily dose level at which withdrawal occurred was lower (100 mg/day) and the range of symptoms experienced was broader than previously recognized. Our most recent set of studies have extended the generality of these previous observations by parametrically characterizing caffeine withdrawal in normal subjects without idiosyncratic histories of caffeine exposure. Manipulation of three parameters (maintenance dose, within-day dosing interval and number of days of chronic caffeine exposure) has been examined under conditions in which subjects received capsules containing either placebo or low to moderate doses of caffeine. Our studies to date clearly document a clinically significant caffeine withdrawal syndrome upon termination of caffeine doses at and below those habitually consumed by a large portion of the general population.

HOW CAFFEINE DEPENDENCE INFLUENCES THE DIAGNOSIS AND TREATMENT OF BEHAVIORAL DISORDERS. John R. Hughes. University of Vermont, Burlington, VT.

The most common adverse behavioral effects of caffeine are anxiety, difficulty concentrating, insomnia, restlessness and tremulousness. These effects appear at daily dosages as low as 400 mg day, a dosage that 30% of Americans consume. The degree to which tolerance to these effects occurs has not been well-tested. These effects could interfere with the diagnosis and treatment of anxiety disorders, attention deficit disorders, agitated and insomniac depressions, sleep disorders, and alcohol and drug withdrawal and intoxication. Caffeine also can interfere with the therapeutic effects of several psychiatric medications. Cessation of caffeine (e.g., upon admittance to an inpatient ward) can cause drowsiness, fatigue and headaches and thereby mimic side-effects from several psychiatric medications.

SYMPOSIUM

Drug Abuse Treatment: Integration of Behavioral and Pharmacological Approaches