Behavioral Pharmacology of Caffeine

SUZETTE M. EVANS

Introduction

Caffeine, a central nervous system (CNS) stimulant, is the most widely used psychotropic drug in the world (Gilbert, 1984). In the United States, more than 85% of adults consume caffeine daily (Gilbert, 1976; Graham, 1978) and the average daily consumption is estimated to be 200 mg (Barone & Roberts, 1984). Caffeine is found in a wide variety of beverages (e.g., coffee, tea, colas), prescription drugs and over-the-counter stimulants, analgesics and cold preparations, and food items such as chocolate. Caffeine has been considered to be a model drug for studying and understanding drugs of abuse (Holtzman, 1990; Rush, Sullivan, & Griffiths, 1995), in part due to caffeine’s widespread use, and because caffeine produces a range of behavioral effects that are common to classic drugs of abuse.

This chapter will focus specifically on those behavioral effects shared with drugs of abuse: subjective (and discriminative) effects, reinforcing effects, development of tolerance, and physical dependence. This chapter is not intended to be a comprehensive review of the entire range of caffeine’s behavioral effects; it is designed to provide an overview of the numerous advances made in this area and emphasize the important role caffeine plays in the lives of many individuals. Specific aspects of caffeine are intentionally ignored in this chapter. For instance, neither caffeine’s mechanism of action nor its effects on cognition and performance are reviewed. Further, the interaction of caffeine with other drugs is not reviewed here; that topic warrants a separate discussion. Readers are referred to several excellent review papers regarding the various behavioral aspects of caffeine (Bättig & Welzl, 1993; Griffiths & Mumford, 1995, 1996; Griffiths & Woodson, 1988a, 1988c; Nehlig, Daval, & Debry, 1992).

Subjective and Discriminative Stimulus Effects of Caffeine

Discriminative Stimulus Effects of Caffeine in Animals

Over the past 35 years, drug discrimination procedures have been developed to examine the discriminative stimulus (DS) effects, or interoceptive cues, of psychoactive drugs in animals. The traditional drug discrimination procedure involves training animals to respond differentially under two different drug conditions. For example, animals are reinforced (usually with food) for responding on one lever following administration of a stimulant
and on another lever following administration of the drug vehicle (usually saline). A wide range of species can be trained to discriminate between psychotropic drugs and a striking concordance has been found between drug classes formed on the basis of similarities in the subjective effects produced in humans and those formed on the basis of similarities as OS in animals (Kamien, Bickel, Hughes, Higgins, & Smith, 1993; Schuster & Johanson, 1988; Schuster, Fischman, & Johanson, 1981).

Several early studies were either unsuccessful at training caffeine as a OS (Overton, 1973) or could establish the discrimination at only high caffeine doses of 125 mg/kg using a shock-escape procedure (Overton & Batta, 1977). Winter (1981) was one of the first to establish a reliable caffeine versus saline discrimination in rats using a training dose of 60 mg/kg. Rats acquired the discrimination within 11–32 training sessions (average of 22 sessions). In the same year, another group showed that rats could learn to discriminate 32 mg/kg caffeine from saline (Modrow, Holloway, & Carney, 1981; Modrow, Holloway, Christensen, & Carney, 1981). Further, Modrow, Holloway, and Carney (1981) showed that caffeine-appropriate responding corresponded to increasing caffeine plasma levels, but caffeine-appropriate responding dropped off rapidly even though caffeine plasma levels were still elevated. Subsequently, numerous studies have been able to establish caffeine as a OS at similar and lower doses and all of the studies to date have used rats (e.g., Holtzman, 1986; Modrow & Holloway, 1985; Mumford & Holtzman, 1991).

A range of xanthines related to caffeine have been tested in animals trained to discriminate caffeine from saline. In rats trained to discriminate a relatively high dose of caffeine (60 mg/kg), the xanthine aminophylline completely substituted for caffeine (Winter, 1981). Several studies have demonstrated that theophylline also substitutes for caffeine in rats trained to discriminate 32 mg/kg caffeine from saline (Carney, Holloway, & Modrow, 1985; Modrow & Holloway, 1985; Modrow, Holloway, & Carney, 1981) and, similarly, caffeine cross-substitutes for theophylline (Carney et al., 1985). Other methylxanthines shared DS effects with caffeine, although theobromine did not (Carney et al., 1985). Interestingly, in rats trained to discriminate either 10 or 30 mg/kg caffeine, a range of methylxanthine drugs did not share DS effects with caffeine (Holtzman, 1986). In that same study, theophylline substituted only partially for caffeine and this was most evident in the group trained to discriminate 30 mg/kg caffeine. Somewhat different results were obtained in another study by the same laboratory (Mumford & Holtzman, 1991). This study trained rats to discriminate either 10 or 56 mg/kg caffeine from saline and several xanthines completely substituted (including theophylline) for the lower training dose of caffeine. In contrast, the only xanthine to share DS effects with the higher training dose of caffeine was theophylline, and these findings did not appear to be a result of tolerance development in rats trained to discriminate 56 mg/kg. Of note, animals trained to the lower dose in the study by Mumford and Holtzman (1991) took twice as long to acquire the discrimination compared with animals trained to the higher dose, although the sessions to criteria for the 10 mg/kg dose was substantially longer than in a previous study that used the same training dose (Holtzman, 1986). Taken together, the ability of other xanthines to share DS effects with caffeine may depend on the training dose of caffeine.

Psychomotor stimulants have been shown to share some DS effects with caffeine, although the results across studies have been inconsistent. Several studies have demonstrated that d-amphetamine (Modrow & Holloway, 1985; Modrow, Holloway, & Carney, 1981), methylphenidate, and nicotine (Modrow, Holloway, & Carney, 1981) do not share DS effects with caffeine in rats trained to discriminate 32 mg/kg caffeine from saline. Other studies have shown that d-amphetamine (Winter, 1981) or cocaine (Mariathasan & Stolerman, 1992) partially substitutes for caffeine. In another study, the ability of psychomotor stimulants, including d-amphetamine, methylphenidate, and cocaine, to substitute for caffeine depended on the training dose (Mumford & Holtzman, 1991).