Pharmacology of Caffeine

JOHN W. DALY

Introduction
The widespread societal use of caffeine-containing beverages has engendered extensive interest in the pharmacological mechanisms underlying the in vivo effects of caffeine, and to a lesser extent the other naturally occurring methylxanthines, namely, theophylline and theobromine. Caffeine is ingested primarily because of mild central stimulant properties, whereby it tends to increase vigilance and defer sleep. Research, therefore, has focused primarily on the pharmacological effects of caffeine relevant to the central nervous system. The pharmacology of methylxanthines, in particular caffeine, has been reviewed in detail (Daly, 1993; Fredholm, Arslan, Johansson, Kuli, & Svenningsson, 1997; Nehlig, 1994) and the present chapter will attempt only a succinct overview without extensive citations of the literature covered in those reviews.

Caffeine is a remarkable drug, whose diuretic and respiratory and central stimulant properties were exhaustively studied for decades before clues as to possible pharmacological sites of action were uncovered. In the late 1950s, caffeine was found to affect calcium-dependent processes (Axelsson & Thesleff, 1958; Bianchi, 1961; Frank, 1960) and to inhibit cyclic AMP phosphodiesterases (Rall & Sutherland, 1958). About 10 years later, caffeine was found to block adenosine receptors (Sattin & Rall, 1970), and in 1979 it was found that caffeine interacted with GABA<sub>A</sub>-receptors (Marangos et al., 1979). These four sites of action remain the most relevant to the pharmacology of caffeine.

Caffeine readily equilibrates throughout the body, including the brain, and has a half-life to 3 to 5 hr in humans. Plasma levels attained in humans after moderate to high consumption of caffeine-containing beverages (100–300 mg/day) are estimated to range from 5 to 20 μM. In addition to its societal use in beverages, caffeine and also theophylline have been used to treat bronchial asthma and neonatal apnea. In such treatments, plasma levels of 50 μM or more are reached. Caffeine at high doses is less likely than theophylline to cause tachycardia, but both are cardiotonic and both increase coronary flow. Both also have diuretic activity and stimulate gastric secretion. Both stimulate lipolysis and inhibit platelet aggregation. The well-recognized somnolytic properties of caffeine led to its former use in the treatment of narcolepsy. Caffeine is used as a flavor enhancer in carbonated beverages and as an adjunct in certain analgesics, diuretics and cold-allergy remedies. Although caffeine and theophylline can induce or exacerbate tremors, theophylline has been proposed for treatment of essential tremor. Caffeine increases duration in electroconvulsive therapy and has been used clinically (Francis &
Fochtmann, 1994). Theobromine, the third naturally occurring methylxanthine, is relatively ineffective as a central stimulant, but has been used in treatment of asthma and as a vasodilator, cardiotonic, and diuretic. There is a wide range of reported interactions of caffeine with other centrally active drugs, in particular those affecting dopamine (amphetamine, cocaine), acetylcholine (nicotine) and GABA (diazepam) receptors or function.

The central activity of caffeine could be termed biphasic. At low doses the effects of caffeine are positive in nature, enhancing alertness, combating fatigue, and improving mood. However, at high doses, caffeine can cause restlessness and anxiety in humans. For humans caffeine consumption ranges between 1 and 5 mg/kg/day, while pharmacological studies in animals usually employ dosages of 5 to 20 mg/kg. In rodents, high doses (>30 mg/kg) of caffeine and theophylline can cause choreiform (dancelike) movements (Nikodijevic, Jacobson, & Daly, 1993a), automutilation, and aggressiveness (Mueller, Saboda, Palmour, & Nyhan, 1982). Convulsions occur at dosages of 200 mg/kg or more. Undoubtedly because of the biphasic action of caffeine, humans tend to titrate consumption only to levels at which the negative effects are not yet manifest, and individuals sensitive to the negative effects avoid caffeine-containing beverages. The term "caffeinism" has been used to describe the symptoms of agitation, anxiety, and insomnia associated with excessive consumption of caffeine. Caffeine in some paradigms appears to have reinforcing effects on self-administration in animals, and reinforcing effects are manifest in humans (Griffiths & Mumford, 1996). Tolerance develops to caffeine, both in humans and animals. A withdrawal syndrome that occurs within the first 24 hours of withdrawal is well documented in humans and usually includes headache, listlessness, irritability, and nervousness.

The mechanisms underlying the pharmacological effects of caffeine remain controversial. Four major hypotheses have been advanced: (1) the mobilization of calcium, (2) the inhibition of phosphodiesterases, (3) the competitive antagonism of adenosine receptors, and (4) effects on GABA<sub>\alpha</sub>-receptors. The release of catecholamines has also been invoked. Caffeine clearly is a drug with multiple sites of action, some of which may still remain undiscovered.

**Mobilization of Calcium**

Discovery of the ability of caffeine to mobilize intracellular calcium stemmed from studies in the late 1950s on caffeine-induced contractions of striatal muscle (Axelsson & Thesleff, 1958; Bianchi, 1961; Frank, 1960). The release of catecholamines by caffeine from adrenal medulla also appears due to mobilization of intracellular calcium (Poisner, 1973). Such effects require millimolar concentrations of caffeine. It is now known that caffeine binds to a site on a cyclic ADP ribose-sensitive calcium channel and thereby enhances calcium-dependent activation of the channel, resulting in a release of calcium from intracellular storage sites in the sarcoplasmic and endoplasmic reticulum. Caffeine is widely used as a research tool for the study of the functional importance of this calcium pool (Ehrlich, Kaftan, Bezprozvannany, & Bezprozvanny, 1994). From the standpoint of relevance to the in vivo pharmacology of caffeine, it should be stressed that caffeine has a very low potency at such calcium channels with thresholds for effects being about 250 mM, while 2 to 20 mM concentrations are required for robust effects. Such a threshold concentration is in the range in which caffeine is a convulsant and even lethal drug. Thus, it seems unlikely that the stimulatory effects of caffeine on calcium release play a major in vivo role in the pharmacology of caffeine.

**Phosphodiesterase Inhibition**

In the late 1950s, the inhibition of phosphodiesterases by caffeine and theophylline was discovered through studies on cyclic AMP systems (Rall & Sutherland, 1958). However, both caffeine and theophylline have proven to be very weak inhibitors of all of the principal phosphodiesterases having IC<sub>50</sub> values of > 100 μM (Ukena, Schudt, & Sybrecht, 1993).