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Caffeine as an Analgesic Adjuvant: A Review of Pharmacology and Mechanisms of Action

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I. Introduction

FROM ANTIQUITY, it has been appreciated that beverages constituted of aqueous extracts of a wide variety of coffee, cola, and cocoa beans have significant stimulant properties (Gilbert, 1981; Rall, 1985). It was, however, not until the turn of the century, when the natural product, caffeine, was isolated and its structure identified in 1875 (Arnaud, 1987), that it was appreciated that a significant proportion of the behavioral and physiological effects produced by these organic extracts was exerted by the alkaloid caffeine. Beverages prepared from these products can contain significant quantities of caffeine. Thus, in a modest 5-oz quantity of coffee, 50 to 150 mg caffeine may be found (Osol and Pratt, 1967). In North America, estimates of daily per capita consumption indicate that approximately 90% of the population consumes an average of approximately 200 mg/day caffeine (Gilbert et al., 1976). Random measurement of plasma caffeine in a clinical outpatient population revealed that 5% of the population had levels greater than approximately 6 μg/ml (Smith et al., 1982).

The ready availability of caffeine extracts and their appreciated stimulant properties led to their incorporation into a variety of popular medicinal products. As with many widely available over-the-counter products, the relative contribution of such agents to the efficacy of the treatment failed to be properly evaluated. In the late 1950s, clinical studies were carried out to examine the effects of caffeine in conjunction with various mildly active analgesics; limited subject populations were used in these studies and appropriate controls were often lacking. Such early investigations led to controversial findings that made it difficult to interpret the contribution, if any, of caffeine to the therapeutic efficacy of these agents (Beaver, 1966, 1981; AMA Drug Evaluations, 1983), a fact reflected by the official position of the United States Food and Drug Advisory review panel on over-the-counter analgesics (Over the Counter Drugs, 1977, 1988).

In the past 10 years, however, an increasing number of controlled clinical trials have produced evidence that caffeine, as a drug, may, indeed, contribute to an amelioration of at least certain pain states. Of equal importance, these clinical observations occur in concert with (*a*) an expanding literature concerning the complex pharmacology of caffeine and its chemical congeners (the methylxanthines; fig. 1) and (*b*) a variety of hypotheses relating to the relevance of peripheral and central methylxanthine-sensitive systems in the initiation and processing of nociceptive information. In the present review, this literature will be considered.

II. Caffeine Metabolism and Kinetics

Caffeine (molecular weight = 194 Da) has a pK_a of 14 and a lipid partition coefficient of 0.85. As a consequence, the molecule exists largely as an undissociated weak electrolyte in the gastric fluid (pH 2 to 3). Kinetic studies have emphasized its rapid and almost complete absorption when given by the oral route. Because caffeine shows a blood to plasma ratio of approximately 1 over a concentration range of 1 to 100 μg/ml (Axelrod and Reichenthal, 1953; Blanchard and Sawers, 1983a) and displays limited protein binding (10% to 35%) (Axelrod and Reichenthal, 1953; Eichman et al., 1962; Desmond et al., 1980; Blanchard and Sawers, 1983b), it has been suggested as being an ideal molecule for comparing drug kinetics across species.

A. Absorption

In all species, there is rapid absorption after oral administration with essentially 100% bioavailability (Arnaud, 1987). In humans, significant levels of caffeine are usually observed at intervals as short as 5 min,

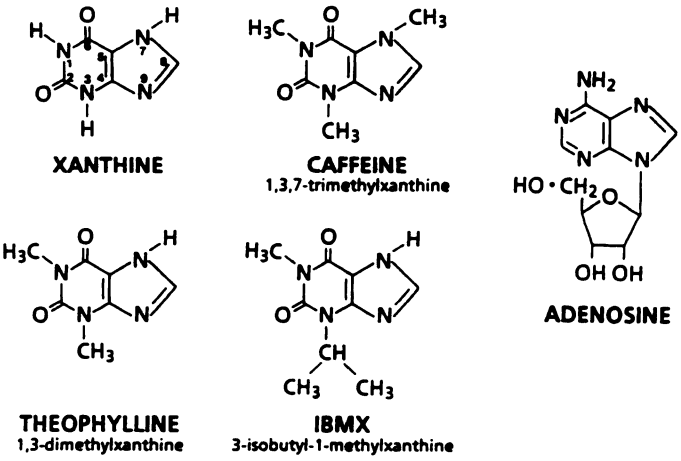

FIG. 1. Chemical structure of caffeine, related methylxanthines, and adenosine.

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whereas peak plasma concentrations are observed approximately 30 to 60 min after oral consumption, although the range can be as wide as 15 to 120 min because of variations in gastric emptying (Grab and Reinstein, 1968; Bonati et al., 1982; Blanchard and Sawers, 1983a). Within 20 min after oral administration, almost 90% of a caffeine dose (175 mg) is cleared from the stomach (Chvasta and Cook, 1971), and plasma concentrations in the range of 5 to 10 μg/ml (20 to 50 μM) are observed. Blanchard and Sawers (1983a,b) observed peak plasma concentrations of 9 μg/ml 33 to 38 min after the oral administration of 5 mg/kg. Bruce et al. (1986) observed peak plasma concentrations of 5.9 and 12.5 μg/ml after the bolus injection of 250 and 500 mg (approximately 3 and 7 mg/kg), respectively. These values have relevance to the range of concentrations normally ingested by humans. As noted before, the daily consumption of caffeine in normal diets has been reported in the range of 3 to 7 mg/kg (Barone and Roberts, 1984). In 17 subjects who consumed coffee and tea, with an average daily consumption of 6.8 mg/kg/day caffeine, mean 24-h plasma levels on the order of 4.4 μg/ml were observed with the range of concentrations during the 24-h sampling period being 1.2 to 9.7 μg/ml (Lelo et al., 1986a).

The volume of distribution of caffeine in humans ranges from 0.5 to 0.7 l/kg, indicating that caffeine is widely distributed and enters intracellular water (Arnaud, 1987; Busto et al., 1989).

B. Metabolism

Caffeine undergoes virtually complete metabolism in all species examined (for review, see Bonati et al., 1985). Only about 1% to 5% of the dose is excreted unchanged, indicating that systemic clearance is essentially equal to metabolic elimination (Axelrod and Reichenthal, 1953; Cornish and Christman, 1957). In humans, there is little evidence for first-pass metabolism. Thus, peak plasma levels and $T_{1/2}$† values were not different after p.o. or i.v. administration of 5 mg/kg caffeine (Blanchard and Sawers, 1983a). In contrast, in rats, there is evidence that caffeine does undergo significant first-pass metabolism (Aldridge et al., 1977; Latini et al., 1978).

Caffeine (1,3,7-trimethylxanthine, 137X) metabolism occurs primarily by demethylation to paraxanthine (1,7-dimethylxanthine, 17X) in humans (Arnaud, 1984; Kalow, 1985; Grant et al., 1987; Bonati and Garattini, 1988; Kalow and Tang, 1991a). This conversion is mediated by cytochrome P450IA2 (Butler et al., 1989; Berthou et al., 1991). Paraxanthine subsequently undergoes two transformations, one of which is 8-hydroxylation (by a cytochrome P450) to form 1,7-dimethylurate (17U); the other metabolic route involves 7-demethylation (by a cytochrome P450) and acetylation (by N-acetyltransferase) to generate either the acetylated ring split product 5-acetylamino-6-formylamine-3-methyluracil or 7-demethylation to form 1-methyxanthine (1X) with a subsequent 8-hydroxylation (by xanthine oxidase) to form 1-methylurate (1U).

The initial 3-demethylation of caffeine to paraxanthine accounts for 84% of caffeine demethylation (Lelo et al., 1986b). Some caffeine also is demethylated to theobromine (3,7-dimethylxanthine, 37X) and theophylline (1,3-dimethylxanthine, 13X), but these represent only minor metabolic conversions, accounting for 12% and 4% of methylations, respectively (Lelo et al., 1986b). Similar routes of metabolism have been reported in dog (Axelrod and Reichenthal, 1953), rabbit (Fabro and Sieber, 1969), rat (Bonati et al., 1985) and mouse (Burg and Stein, 1972; Burg and Werner, 1972). In mouse and rat, the distribution of metabolites is more diffuse than it is in humans (Bonati et al., 1985; Bonati and Garattini, 1988).

C. Clearance

The plasma $T_{1/2}$ of caffeine in humans is generally 3 to 5 h (Bonati et al., 1985; Kalow, 1985; Busto et al., 1989). Systematic studies have shown that $T_{1/2}$ (h) values vary with species: mouse, 0.7; rat, 0.8; rabbit, 1.6; and monkey, 3.2 (Bonati et al., 1985).

The kinetics of caffeine have been reported to be linear in humans over the dose ranges that have been examined (50 to 750 mg, p.o.; Newton et al., 1981). In rodents, nonlinear kinetics have been reported with doses as low as 10 mg/kg. Thus, after i.p. administration, a numerical increase in plasma $T_{1/2}$ and a reduced volume of distribution was observed as the dose was increased from 20 to 40 mg/kg, i.p., in mice (Kaplan et al., 1990a). Such dose-dependent kinetics have not been reported at lower doses (<10 mg/kg) by other investigators examining rodents or primates (Garattini, 1981; Latini et al., 1980).

D. Blood-Brain Transfer

Kinetic studies in rodents have emphasized that plasma caffeine and metabolite levels closely reflect brain concentrations. Kaplan et al. (1989, 1990a,b) observed that the slope of the regression line obtained by plotting brain versus plasma concentrations was 1.0, 0.4, 0.3, and 0.5 for caffeine, theophylline, paraxanthine, and theobromine, respectively, during a 1- to 4-h period after 40 mg/kg, i.p. Zhi and Levy (1990), using a continuous i.v. infusion paradigm, observed that the regression line, when plotting brain (or CSF) to serum concentrations of caffeine over a range of approximately 0.5 to 40 μg/ml, was linear and had a slope of about 0.6, suggesting that caffeine, within the plasma concentration ranges used, moves into the brain by simple diffusion. McCall et al.

† Abbreviations: $T_{1/2}$, half-life; CSF, cerebrospinal fluid; NAPQI, N-acetyl-*p*-benzoquinone imine; CNS, central nervous system; ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; cyclic AMP, cyclic adenosine 3′,5′-monophosphate; GABA, γ-aminobutyric acid; NSAID, non-steroidal anti-inflammatory drug; i.t., intrathecal; i.c.v., intracerebroventricular; p.o., by mouth; NMDA, N-methyl-D-aspartate; NA, noradrenaline; PGE, prostaglandin E.

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(1982), using the Oldendorf rat carotid-brain clearance model (movement into brain following direct intracarotid injection), found that caffeine appeared to enter the brain by both a simple diffusion process and by a low-affinity (K_m = 5.4 mM) saturable transport.

The movement of caffeine into the brain following direct intracarotid injection is rapid and reflects uptakes that are similar to free water distribution (86%; Oldendorf, 1971; McCall et al., 1982), with nearly complete clearance following a single passage. Consistent with this rapid movement, significant brain levels are observed within 5 min, even after oral administration of caffeine, with peak levels being observed within 30 min (Latini et al., 1978).

With regard to clearance from brain, at low oral doses (1 mg/kg, p.o.), the $T_{1/2}$ of caffeine in brain and plasma are identical (130 min), whereas at higher doses, the $T_{1/2}$ in brain increases significantly (10 mg/kg, p.o., 189 versus 81 min, respectively; Latini et al., 1978). After i.p. injection, peak plasma and brain levels were observed at the earliest times examined (5 min) and were approximately 30 μg/ml and 40 μg/g, respectively. The $T_{1/2}$ in brain and plasma did not differ statistically (1.3 and 1.6 h, respectively; Kaplan et al., 1989, 1990a,b).

In adult humans, there are no data regarding the redistribution of caffeine into brain or CSF. However, there is no reason to believe that humans differ from other animals in this regard. Moreover, caffeine has been shown to achieve significant CSF to blood ratios in newborns, indicating that, as in animals, this substance gains significant and rapid access to CNS sites (Somani et al., 1980).

E. Factors Governing Caffeine Disposition

In addition to species differences, a number of factors appear to contribute to the absorption and kinetics of caffeine.

1. Age. Rates of caffeine clearance are similar in older and younger adults (Axelrod and Reichenthal, 1953; Parsons and Neims, 1978; Parsons et al., 1976; Aranda et al., 1977; Blanchard and Sawers, 1983b). In neonates, there is evidence that the metabolic clearance of caffeine occurs more slowly because of the lack of development of the mixed function oxidase systems. Thus, the $T_{1/2}$ was reported to be 65 to 103 h in preterm infants, 82 h in term infants, 14 h in 3- to 4-month-old infants, and 2.6 h in 5- to 6-month-old infants; the latter $T_{1/2}$ corresponds to values reported in adults (generally 3 to 5 h) (Arnaud, 1987).

2. Genetics. Caffeine metabolism is subject to the polymorphism associated with N-acetyltransferase, i.e., it exhibits both fast and slow acetylation rates (Grant et al., 1983; Kalow, 1985). Ethnic groups display significant differences in the proportion of the population regarded as slow acetylators, as well as in the generation of other metabolites (Grant et al., 1983; Kalow, 1985). The determination of caffeine metabolite ratios can serve as a probe for acetylation phenotyping (Grant et al., 1983; Tang et al., 1991).

3. Exercise. In humans given oral doses of caffeine (250 mg), moderate exercise increased the peak plasma concentration and reduced the $T_{1/2}$ (4.0 to 2.3 h) (Collomp et al., 1991). This reduced $T_{1/2}$ appears paradoxical because exercise reduces hepatic blood flow and caffeine is largely metabolized in the liver, but such changes in metabolism have also been described for antipyrine which is also cleared in a manner similar to caffeine (Swartz et al., 1974).

4. Pregnancy. A prolongation of the $T_{1/2}$ of caffeine (2.5 to 7 times) occurs during late pregnancy (Knutti and Kurihara, 1987; Parsons and Pelletier, 1982). There is no placental barrier to the passage of caffeine from the mother to the fetus (Maickel and Snodgrass, 1973).

5. Disease. Caffeine is metabolized primarily by liver enzymes (Berthou et al., 1991). It is, therefore, not surprising that liver disease (cirrhosis, viral hepatitis, alcohol-induced fatty liver) can decrease the rate of caffeine demethylation in humans (Kalow, 1985).

6. Smoking/enzyme inducers. Smoking stimulates caffeine clearance, such that the $T_{1/2}$ may be reduced by as much as one-half (Parsons and Neims, 1978; May et al., 1982). The mechanism underlying this effect is likely metabolic, reflecting the induction of hepatic enzymes such as cytochrome P450IA2 by smoking (Kalow and Tang, 1991b). Polycyclic aromatic hydrocarbons, such as polychlorinated or polybrominated biphenyls, or rifamprin (an antitubercular drug that is known to be a powerful enyzyme inducer) will similarly increase the rate of demethylation of caffeine in humans (Campbell et al., 1987; Lambert et al., 1990).

7. Drugs. A variety of coadministered drugs are reported to lead to an impairment of caffeine elimination, often by competition at the enzymatic level. These include oral contraceptives (Patwardhan et al., 1980; Callahan et al., 1983), cimetidine (Desmond et al., 1980; May et al., 1982), disulfiram (Beach et al., 1986), alcohol (Mitchell et al., 1983; George et al., 1986), and idrocilamide (Brazier et al., 1980).

F. Effect of Caffeine on Drug Kinetics and Metabolism

Caffeine has been shown to exert a number of effects on organ systems that may alter the subsequent absorption and metabolism of other agents.

1. Caffeine effects on gastric absorption. Caffeine can lower gastric acidity by directly stimulating parietal cells (Debas et al., 1971; Syed, 1976). Early studies revealed that caffeine (100 mg/kg, p.o.) would reduce gastric emptying in rats, in part by a relaxation of smooth muscle (Siegers et al., 1972). In humans, such effects on smooth muscle can result in the reduction of esophageal sphincter tone, which potentially can facilitate gastric reflux (Sacre and Vandenplas, 1987; Skopnik et al., 1990). The

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actions of caffeine on secretion are likely to be complex, because it has also been shown that adenosine will increase basal H^+ secretion in isolated gastric glands, and this effect is antagonized by caffeine (Gil-Rodrigo et al., 1990). The lowering of pH would facilitate the diffusion of agents whose pK_a rendered them unionized in an acidic environment (e.g., aspirin, for which the optimal absorption is in the pH range of 2.5 to 4.5).

2. Caffeine effects on organ perfusion. Caffeine specifically, and methylxanthines in general, will reduce liver blood flow (Onrot et al., 1986); this action is likely mediated by an antagonistic effect of caffeine on the dilatory effects of adenosine on hepatic artery and portal vein (Lautt and McQuaker, 1989; Sawmiller and Chou, 1990). The reduction in hepatic circulation induced by caffeine would serve to reduce the metabolic clearance of agents undergoing primary elimination through hepatic metabolism. Caffeine and methylxanthines increase the flow in the microcirculation of the gastric mucosa, an action secondary to its effects on cyclic AMP (Beubler and Lembeck, 1976). In ileal and jejeunal loops, caffeine can increase drug absorption as a result of an apparent increase in mesenteric blood flow (Hsu et al., 1987; but see Lautt, 1990).

3. Effects on disposition of analgesic drugs. a. ASPIRIN. In rodent studies, caffeine (5 mg/kg) had no effect on aspirin plasma or brain levels after oral administration (Collins et al., 1979). In humans, concurrent oral administration of caffeine (120 mg) with aspirin (650 mg) has been shown to increase the peak plasma concentration (50 to 58 μg/ml) by about 20%. The area under the plasma concentration-time curve was increased by 7%. There was no change in plasma $T_{1/2}$, volume of distribution, or clearance of salicylate (Yoovathaworn et al., 1986). Similar results were observed by Dahanukar et al. (1978). The mechanism for this enhanced availability is not known; however, the optimum gastric pH for aspirin absorption is between 2.5 and 4, and caffeine, as noted before, facilitates gastric acid secretion and enhances gastric perfusion.

b. ACETAMINOPHEN. After oral administration in rats, Siegers (1973) reported that caffeine (10 to 100 mg/kg) would reduce plasma levels of acetaminophen in a dose-dependent fashion, presumably by a reduction in the rate of gastric clearance. In contrast, in mice, concurrent administration of caffeine (100 mg/kg, i.p.) with acetaminophen (200 mg/kg, i.p.) can produce a significant increase in acetaminophen plasma levels and an increase in the $T_{1/2}$ (0.39 to 0.53 h; Price and Gale, 1987). These augmented plasma levels of acetaminophen may arise from an effect of caffeine on the metabolic clearance of acetaminophen. Metabolism of acetaminophen can occur through a cytochrome P450 pathway, producing a reactive metabolite, NAPQI, that has been implicated in the hepatotoxicity observed following the ingestion of very high doses of acetaminophen (Mitchell et al., 1973; Hinson, 1980). Results of earlier studies were controversial, demonstrating that caffeine had both a protective effect on acetaminophen-induced hepatotoxicity in mice (Gale et al., 1986, 1987) and a facilitatory effect on such toxicity in rats (Sato et al., 1985).

The effect of caffeine appears to depend in part on the induction state of the liver. Thus, caffeine reduces acetaminophen-induced hepatotoxicity in 3-methylcholanthrene-induced rats but increases acetaminophen-induced hepatotoxicity in phenobarbital-induced rats (Kalhorn et al., 1990). In in vitro studies, in which caffeine is added directly to microsomal preparations, caffeine enhances the formation of NAPQI in uninduced or phenobarbital-induced rats (Nouchi et al., 1986; Lee et al., 1991; cf. Sato and Izumi, 1989). In microsomes from 3-methylcholanthrene-induced rats, caffeine produces a biphasic effect, reducing NAPQI formation to <1.5 mM but enhancing formation at higher concentrations (Lee et al., 1991). The biphasic effect reflects two distinct actions of caffeine: inhibition of cytochrome P450IA1, which is induced by 3-methylcholanthrene and is an efficient oxidizer of acetaminophen to NAPQI (Harvison et al., 1988), and activation of cytochrome P450IIIA2, which is induced by phenobarbital but in the absence of caffeine is only slightly effective in oxidizing acetaminophen to NAPQI (Lee et al., 1991). The relevance of these interactions to the human situation remains to be determined.

c. IBUPROFEN. In a limited study, it was shown that ibuprofen (200 mg) showed a modest increase in its maximum plasma concentration and area under the curve after 200 mg, but not 100 mg, caffeine (Bottini et al., 1986).

d. MORPHINE. In rats, acute administration of caffeine (100 mg/kg) has been reported to elevate plasma and brain concentrations of morphine (Misra et al., 1985). However, the concentrations of morphine metabolites in plasma and liver or the proportion of metabolites to unchanged morphine in liver did not change, suggesting that morphine metabolism was unchanged. In mice, neither acute administration of caffeine (40 mg/kg) (Ahlijanian and Takemori, 1985) nor chronic administration (14 days) in drinking water (Ahlijanian and Takemori, 1986a) altered brain levels of morphine.

G. Summary

Caffeine displays a rapid and almost complete absorption from the stomach after oral administration. In humans, after oral doses in the range of 1 to 3 mg/kg (60 to 180 mg total dose), plasma levels on the order of 5 to 10 μg/ml or 30 to 50 μM are routinely observed. In the stomach, assuming a volume of 100 ml, local drug concentrations after ingestion could be in the millimolar range. Such levels have particular significance when considering the possible pharmacological mechanisms whereby caffeine exerts its several actions. Because of

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its lipophilicity and limited protein binding, caffeine readily crosses the blood-brain barrier, giving brain and CSF levels that differ little from those measured in plasma. Although there are species differences, the molecule is largely metabolized by mixed function oxidases in the liver. Caffeine has a plasma $T_{1/2}$ in the range of 3 to 5 h. The $T_{1/2}$ of caffeine is increased by pregnancy, liver disease, drugs (such as oral contraceptives, alcohol, and cimetidine), and particularly in the neonate. Conversely, caffeine clearance may be enhanced by exercise or smoking. Caffeine, by reducing organ perfusion (as in the liver), may reduce the metabolism of concurrently administered agents such as acetaminophen. On the other hand, in the gastrointestinal tract, the prosecretory effect and enhancement of local tissue perfusion by caffeine can augment absorption of other agents by, respectively, lowering gastric acidity and increasing the local gastrointestinal clearance of agents such as aspirin.

III. Pharmacology of Caffeine

In this section, the pharmacological actions of caffeine, in particular, and the methylxanthines, in general, will be reviewed. The potential involvement of these pharmacological actions of caffeine in its effects on peripheral and central mechanisms of nociceptive processing will be considered in sections VII and VIII, respectively.

A. Overview of Caffeine and Methylxanthine Actions

Caffeine and theophylline exert a variety of pharmacological actions at diverse peripheral and central sites. Methylxanthines have antiasthmatic actions, cause smooth muscle relaxation, stimulate the CNS, stimulate cardiac muscle, and produce diuretic actions (Arnaud, 1987; Rall, 1990). An understanding of the cellular basis of these diverse actions has undergone revision within the last decade. Following the discovery of the cyclic AMP system (approximately 1960) and the observation that methylxanthines could inhibit phosphodiesterase activity and elevate cyclic AMP levels in the cell particularly following hormone or neurotransmitter stimulation, the diverse actions of methylxanthines were understood in terms of phosphodiesterase inhibition (Ritchie, 1975). This hypothesis was attractive because the ubiquity of cyclic AMP and phosphodiesterase enzymes could explain why methylxanthines affected so many different tissues. However, this action generally requires concentrations of 0.1 to 1 mM. Following therapeutic doses or ingestion of caffeine and theophylline via beverages, plasma levels are generally 10 to 50 μM (section II).

Methylxanthines act as competitive adenosine receptor antagonists in the 10 to 100 μM range, and antagonism of the various actions of adenosine is currently considered to be the more significant mechanism by which caffeine and theophylline exert their spectrum of pharmacological actions (Fredholm, 1980; Phillis and Wu, 1981; Daly, 1982; Rall, 1982). This mechanism has been directly implicated in the actions of caffeine and theophylline in humans (Biaggioni et al., 1991). Other actions, such as phosphodiesterase inhibition and Ca^{2+} mobilization, may seem less likely to contribute to the pharmacology of caffeine in view of the higher doses required to produce the effect. However, these actions may contribute to the pharmacology of caffeine at certain sites when a particular route of administration produces a local higher concentration of caffeine or theophylline. Alternatively, such actions may contribute to toxic effects of these agents.

B. Adenosine Receptor Antagonism

Purine receptors are classified as nucleoside (P1) or nucleotide (P2) receptors (Burnstock, 1978). Adenosine (P1 purine) sites are further classified as A1 or A2 receptors. The original classification of adenosine receptors was based on respective effects on the adenylate cyclase system: lower doses of adenosine inhibited adenylate cyclase and decreased cyclic AMP levels via an A1 receptor, and higher doses of adenosine stimulated adenylate cyclase and enhanced cyclic AMP levels via an A2 receptor (Londos and Wolff, 1977; Van Calker et al., 1979). The involvement of adenylate cyclase in various actions of adenosine is not, however, always apparent. Currently, A1 and A2 receptors are classified on the basis of differential rank ordering of potency of several adenosine analogues (A1: cyclopentyladenosine > cyclohexyladenosine > *R*-phenylisopropyl adenosine > 2-chloroadenosine > N-ethylcarboxamide adenosine > *S*-phenylisopropyl adenosine; A2: N-ethylcarboxamide adenosine > 2-chloroadenosine > *R*-phenylisopropyl adenosine > cyclopentyladenosine > *S*-phenylisopropyl adenosine; Daly, 1985; Williams, 1989). Subdivision of the A1 (A1a and A1b) receptor has been proposed on the basis of the order of potency of agonists, particularly CV-1674 (Gustafsson et al., 1989), and of the A2 receptor (A2a and A2b) on the basis of the differing affinities of N-ethylcarboxamide adenosine at different sites (Bruns et al., 1986). An additional receptor, the A3 site, which regulates Ca^{2+} fluxes, also has been proposed (A3: cyclohexyladenosine, L-phenylisopropyl adenosine, N-ethylcarboxamide adenosine > 2-chloroadenosine; Ribeiro and Sebastião, 1986). An intracellular site on the catalytic subunit of adenylate cyclase, which inhibits the enzyme activity, has been identified (Haslam et al., 1978), but its physiological role has yet to be determined.

Effects of adenosine on the cyclic AMP transduction system are mediated via nucleotide-binding proteins (G-proteins) (Schramm and Selinger, 1984). Effects on cyclic AMP are not, however, the only mechanism for signal transduction by adenosine. Thus, adenosine modulates K^+ and Ca^{2+} channel activity in neural and non-neural tissue (reviewed by Fredholm and Dunwiddie, 1988; Cooper and Caldwell, 1990). In many cases, these actions of adenosine are mediated via G-proteins, without the involvement of cyclic AMP (Dolphin and Pres-

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twick, 1985; Trussell and Jackson, 1987; Fredholm and Dunwiddie, 1988; Cooper and Caldwell, 1990). Adenosine also modulates the effects of histamine on inositol phospholipid metabolism, with both inhibition (rat; Petcoff and Cooper, 1987) and augmentation (guinea pig; Hollingsworth et al., 1986; Hill and Kendall, 1987) of metabolism having been reported to occur. Such effects may be secondary to alterations in intracellular Ca^{2+} fluxes (Cooper and Caldwell, 1990).

Caffeine is a competitive adenosine receptor antagonist at adenosine receptors. Antagonism is observed at concentrations of 10 to 100 μM, and there is little selectivity for A1 or A2 receptors. In binding studies, the K_i of caffeine at A1 sites ranges from 27 to 55 μM, and the K_i at A2 sites ranges from 46 to 50 μM (Schwabe et al., 1985; Daly et al., 1986; Bruns et al., 1986). Theophylline is slightly more potent as an adenosine receptor antagonist (A1: K_i = 8.5 to 14 μM; A2: K_i = 11 to 25 μM) but exhibits a similar lack of selectivity between receptor subtypes. A similar range of concentrations of caffeine and theophylline (10 to 300 μM) has been shown to block functional effects of A1 and A2 agonists at pre- and postsynaptic sites in the CNS and peripheral nervous system (see references in Fredholm and Hedqvist, 1980; Ribeiro, 1991). The adenosine A3 receptor is sensitive to similar concentrations of methylxanthines (Ribeiro and Sebastião, 1986). The intracellular adenosine site modulating adenylate cyclase is not sensitive to methylxanthines.

C. Phosphodiesterase Inhibition

Methylxanthines have been known for some time to inhibit cyclic nucleotide phosphodiesterase activity (Sutherland and Rall, 1958; Butcher and Sutherland, 1962). Multiple forms of phosphodiesterase have been shown to occur, differing in substrate specificity (cyclic AMP versus cyclic guanosine 3′,5′-monophosphate), subcellular localization (soluble versus membrane bound), and Ca^{2+}/calmodulin sensitivity (Weishaar et al., 1985; Nicholson et al., 1991a). These forms have recently been classified into five distinct subfamilies (Beavo and Reifsnyder, 1990; Nicholson et al., 1991a). Although different forms of phosphodiesterase can be inhibited differentially by various agents (Weishaar et al., 1985; Nicholson et al., 1991a), both caffeine and theophylline exhibit a wide spectrum of activity. Thus, caffeine and theophylline inhibit Ca^{2+}-dependent and Ca^{2+}-independent and soluble and membrane-bound forms of phosphodiesterase from brain tissue, with concentrations producing 50% inhibition values of 480 to 750 μM for caffeine and 350 to 1000 μM for theophylline (Smellie et al., 1979; Choi et al., 1988). Inhibition of phosphodiesterases by caffeine generally requires concentrations of 0.1 to 1 mM, which typically exceeds the concentrations observed in blood following normal oral dosing. However, a limited amount of phosphodiesterase inhibition can occur at concentrations of 50 μM theophylline, and it was noted that substantial lipolytic effects occurred at concentrations of xanthine derivatives producing <20% inhibition of phosphodiesterase activity (Beavo et al., 1970). Thus, some caution is required when considering methylxanthines as exerting their effects simply as adenosine receptor antagonists (Daly, 1982).

D. 5′-Nucleotidase Inhibition

5′-Nucleotidase occurs as both a soluble and membrane-bound ectoenzyme (Schrader, 1991). The intracellular soluble form may be involved in the formation of intracellular adenosine from AMP, whereas the ectoenzyme catalyses the breakdown of AMP outside the cell, and both forms may contribute to regulating extracellular levels of adenosine (section VII.B.2). Caffeine and theophylline inhibit both forms of 5′-nucleotidase activity in a competitive manner (Tsuzuki and Newburgh, 1975; Fredholm and Lindgren, 1983). Inhibition occurs between 0.1 and 1 mM. The order of potency of several methylxanthines does not correspond to their actions as adenosine receptor antagonists or phosphodiesterase inhibitors. This pharmacological action may be of consequence under conditions in which AMP accumulations occur, such as increased hydrolysis of ATP or decreased ATP synthesis.

E. Calcium Movements

The effects of caffeine on Ca^{2+} movements in the cell were first studied in skeletal muscle. In in vitro preparations, caffeine augments the twitch height and at a higher concentration produces a sustained contracture of skeletal muscle (Bianchi, 1968; Lüttgau and Oetliker, 1968). The contracture results from an increased intracellular availability of Ca^{2+} because caffeine inhibits ATP-dependent Ca^{2+} uptake into, and releases accumulated Ca^{2+} from fragmented, skeletal muscle, sarcoplasmic reticulum (Weber and Herz, 1968; Johnson and Inesi, 1969; Su and Hasselbach, 1984; Chapman and Tunstall, 1988). This releasing action of caffeine occurs via an action on specific Ca^{2+} channels in the sarcoplasmic reticulum (Pessah et al, 1987). Both inhibition of uptake and release of Ca^{2+} occur in the concentration range of 1 to 25 mM. An additional effect of caffeine on Ca^{2+} release in skeletal muscle also may occur whereby caffeine enhances Ca^{2+}-induced Ca^{2+} release (Konishi and Kurihara, 1987; Sitsapesan and Williams, 1990) at concentrations lower than those required to directly induce release (0.2 to 2 mM).

Caffeine appears to produce similar effects on Ca^{2+} movements within neurons. Thus, caffeine (5 to 15 mM) reduces Ca^{2+} uptake into brain microsomal vesicles (Trotta and Freire, 1980) and stimulates Ca^{2+} release from endoplasmic reticulum from lysed brain synaptosomes (Mekhail-Ishak et al., 1987). In intact neurons, caffeine (10 mM) increases intracellular Ca^{2+} levels by causing release from an intracellular site in dorsal root

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ganglion cells (Neering and McBurney, 1984; Thayer et al., 1988b) and in sympathetic neurons (Lipscombe et al., 1988). Caffeine-sensitive stores are most apparent in cell bodies, being much less pronounced in cell processes in intact cells (Thayer et al., 1988b; Lipscombe et al., 1988). However, caffeine-induced release of Ca^{2+} from brain synaptosomes has been demonstrated directly (Martinez-Serrano and Satrustegui, 1989). The Ca^{2+} pool in neurons that responds to caffeine differs from that which responds to inositol triphosphate and is susceptible to blockade by ryanodine (Thayer et al., 1988a,b; Martinez-Serrano and Satrustegui, 1989). The brain ryanodine receptor has recently been proposed to function as a caffeine-sensitive Ca^{2+} release channel (McPherson et al., 1991). It appears that caffeine can alter Ca^{2+} availability in both the cell body and nerve terminal portions of the neuron, but it is not clear to what extent this action contributes to the pharmacology of caffeine following systemic administration in view of the doses required to produce this effect.

F. Other Pharmacological Interactions of Caffeine

1. Benzodiazepine/γ-aminobutyric acid A receptors. Certain central effects of caffeine have been proposed to be due to an interaction with benzodiazepine receptors (Marangos et al., 1979a). Methylxanthines have been reported to competitively inhibit benzodiazepine binding (Marangos et al., 1979b; Boulenger et al., 1982; Weir and Hruska, 1983) and to augment the number of benzodiazepine-binding sites (Kaplan et al., 1989). Caffeine antagonizes several central effects of diazepam (Polc et al., 1981). However, the doses of caffeine required to inhibit benzodiazepine binding are high (0.1 to 2 mM; concentrations producing 50% inhibition, 400 to 800 μM), and some investigators have not observed alterations in benzodiazepine binding (Lopez et al., 1989). There is the distinct possibility that the observed antagonism is due to opposing physiological actions (Roache and Griffiths, 1987).

Other observations indicate that caffeine may interact with the $GABA_A$ receptor-Cl^- channel complex in a more indirect manner. Thus, caffeine decreases muscimol-stimulated Cl^- uptake (Lopez et al., 1989), suggesting an impairment of receptor-channel coupling. In addition, caffeine-induced Ca^{2+} release from an intracellular store has been shown to block the $GABA_A$-induced inward current on primary afferent neurons (Desaulles et al., 1991).

2. Interaction with noradrenaline. Caffeine and theophylline potentiate the response to NA in the vascular system by inhibiting extraneuronal uptake and metabolism by catechol-O-methyl transferase (Kalsner, 1971; Kalsner et al., 1975). This action occurs at pharmacologically relevant doses (150 μM) and may contribute to the effects of methylxanthines in the vascular system.

3. Arachidonic acid metabolites. Caffeine has been reported to have intrinsic anti-inflammatory actions and in lower doses potentiates the anti-inflammatory action of a number of cyclooxygenase inhibitors (Vinegar et al., 1976; Seegers et al., 1981). However, caffeine does not inhibit prostaglandin synthesis itself in a number of in vitro preparations; nor does it enhance inhibition produced by aspirin (Vinegar et al., 1976). In the isolated perfused heart, adenosine increases prostacyclin production by a methylxanthine-sensitive mechanism (Ciabattoni and Wennmalm, 1985; Karwatowska-Prokopczuk et al., 1988). However, this may not necessarily reflect a direct coupling of adenosine receptors to the arachidonic acid transduction system, because the increases in prostacyclin levels were thought to be secondary to changes in blood flow induced by adenosine. Interestingly, 3-isobutyl-1-methylxanthine, which, like caffeine, is a broad-spectrum phosphodiesterase inhibitor (Smellie et al., 1979; Davis, 1984) and adenosine receptor antagonist (Daly et al., 1981), may directly inhibit phospholipase A activity and arachidonic acid release, as well as cyclooxygenase activity (0.5 to 1 mM) (Whorton et al., 1985).

In view of the role of arachidonic acid products in the peripheral signaling of tissue injury (section IV.A), further examination of the effects of both caffeine and adenosine on the generation of arachidonic acid products in tissues and cells, which are specifically relevant to sensory nerve terminals, appears warranted.

G. Summary

Methylxanthines exert a spectrum of pharmacological actions. Initially, such actions were considered to occur because of phosphodiesterase inhibition at various central and peripheral sites. However, since the early 1980s, methylxanthine pharmacology has been understood in terms of inhibition of the various actions of adenosine. Adenosine acts at both A1 and A2 receptors, and caffeine has a comparable affinity for both receptor populations (K_i 10 to 100 μM). Although less well studied, significant effects on monoamine uptake may be exerted at these concentrations. These effects occur at therapeutic concentrations and concentrations encountered following ingestion of caffeine in beverages. Other actions of methylxanthines, such as phosphodiesterase inhibition, Ca^{2+} mobilization, or 5′-nucleotidase inhibition require concentrations of caffeine in excess of 100 μM. Although these actions are less likely to contribute to the actions of caffeine because of this higher dose requirement, they must be considered as potential mechanisms because (*a*) physiological consequences may accrue from a limited interaction with such systems, (*b*) following certain local routes of administration (e.g., spinal cord after i.t. administration; stomach and gastrointestinal tract after oral administration), considerably higher local concentrations may be encountered, and (*c*) they may contribute to toxic actions.

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IV. Analgesic and Adjuvant Actions of Caffeine in Humans

A. Clinical Studies with Caffeine

Within this context, three important issues arise: (*a*) Does caffeine alone influence pain behavior? (*b*) Does caffeine exert an adjuvant effect? (*c*) What are the characteristics of the pain state that define its analgesic efficacy? The current literature regarding clinical studies that have been carried out using caffeine as an adjuvant to the analgesic actions of a variety of NSAIDs is summarized in table 1.‡

1. Effects of caffeine alone on pain behavior in humans. Although a significant number of studies have been published regarding the effects of caffeine on psychomotor performance (section VI), there have been relatively few investigations that have defined its actions as an analgesic when given alone. Forbes et al. (1990) failed to find caffeine (64 mg) different from placebo in a study in which pain resulting from dental extraction was examined. Ward et al. (1991) observed that 130 mg, but not 65 mg, caffeine was superior to placebo in alleviating nonmigranous headaches.

2. Analgesic adjuvant actions of caffeine in humans. Of the entries in table 1, there are 27 entries reflecting published work in which, at a minimum, there was (*a*) a simple "blinded" comparison paradigm; (*b*) an NSAID, an NSAID + caffeine at a dose of 60 mg or more, and a placebo; (*c*) patient populations of approximately 30 or more patients per group; and (*d*) a statistical analysis. These studies have involved pain models of principally postpartum pain, postsurgical pain (dental extraction), and headache. Of these, 14 entries obtained a greater magnitude or incidence of pain relief with the numerical differences in drug effect (pain relief) reaching a statistical significance of $P \leq 0.05$ with the addition of caffeine as compared to NSAID alone.

When bioassay paradigms are used and at least two doses of NSAID are administered alone and in the presence of caffeine, 11 entries can be considered. In these studies, dose-dependent increases in pain relief for the NSAID alone have been reliably observed. The addition of caffeine to the formulation typically results in a parallel leftward shift in the dose-response curve. An example of this is displayed in figure 2 for caffeine and ibuprofen.

As reviewed in table 1, the relative potencies, i.e., the degree of leftward shift, examined in the presence of caffeine as compared to the absence of caffeine range from 1.29 to 1.92 for acetaminophen, 1.55 to 1.58 for acetaminophen and aspirin combinations, and 1.0 to 2.9 for ibuprofen. As indicated in table 1, all but a few of these bioassay studies display potency ratios which are statistically significant.

Perhaps the most comprehensive population examination of the effects of the addition of caffeine was the early report by Laska et al. (1984). Using population statistic techniques generically referred to as meta-analysis (Sacks et al., 1987), these investigators analyzed the results of 30 studies in which aspirin, acetaminophen, or a combination of the two NSAIDs was given alone or jointly with caffeine. Many of these studies were not published in the peer-reviewed literature and thus cannot be examined separately. Based on these independent investigations, potency estimates in postpartum, headache, and postsurgical (dental) pain states were obtained. These pooled estimates from Laska et al. (1984) are presented in table 2. As indicated, the addition of caffeine resulted in a clear increase in the activity of the NSAID dosing regimen.

B. Factors Influencing Efficacy of Caffeine as an Analgesic Adjuvant

Based on our appreciation of pharmacodynamics and the functional properties of analgesics, it is probable that several factors may influence the apparent activity of caffeine. These include (*a*) dose, (*b*) test stimulus (pain state, intensity), and (*c*) the characteristics of action of the codrug.

1. Caffeine dose. Investigators in early studies, in which the effects of caffeine on modifying human pain states were examined and in which blinded paradigms were used with some controls, frequently failed to observe any additional effect of caffeine (Currier and Westerberg, 1958; Marrs et al., 1959; Frey, 1961; Cass and Frederik, 1962; DeKornfeld et al., 1962; Bauer et al., 1974; Moertel et al., 1974). Significantly, many of these early studies may have suffered from several limitations, including small group size and lack of test sensitivity (see comment by Beaver, 1984; Over the Counter Drugs, 1977). Alternately, in many of these studies, commercially available formulations of the historically accepted quantity of a 0.5 gr (32 mg) caffeine were typically used. It is significant that the normal daily consumption of caffeine through routine dietary consumption frequently exceeds that used in these early studies. Wallenstein (1975), in an early commentary, suggested that at doses of <60 mg caffeine might not evoke a detectable effect. This observation appears borne out by subsequent investigations carried out first by Booy (1972), who used doses of 50 and 100 mg, and subsequently by many others who reported a contributory effect of caffeine. Simple comparison studies in which an effective dose of NSAID (acetaminophen, approximately 500 mg; aspirin, approx-

‡ The term NSAID is used in this review to refer to those nonopioid, nonsteroidal agents that have classically been considered to have antipyretic actions and to act peripherally to exert a mild antinociceptive effect, i.e., aspirin-like drugs (Flower et al., 1985). These include agents such as acetylsalicylic acid, acetaminophen, and ibuprofen. As will be emphasized in section IX, such a definition is only partially accurate because acetaminophen, for example, although antipyretic and not a steroid, does not significantly reduce signs of inflammation and has poor effects on cyclooxygenase. Nevertheless, by convention, it is included in this generic category.

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TABLE 1

*Summary of clinical studies examining the analgesic adjunctive effects of caffeine**

Study no.	Authors†	Pain population (no.)	Study comments	Caffeine dose (mg)	Agent (doses)	Outcome	Relative potency + caffeine‡
	Mixed postsurgical/cancer						
1	Marrs et al., 1959[a]	Mixed/chronic (55)	DB	32	[AS (333)]; [AS (227) + PH (162) + C]; [COD (32)]; P	AS; P; (ASA + PH +C); COD	[A]
2	Cass and Frederik, 1962[a]	Mixed/chronic (25)	DB	30	[AS (650)]; [AS (320) + PH (320) + C]; P (×4/d)	AS; (ASA + PH + C) > P	[A]
3	Moertel et al., 1974	Cancer (100)	DB	65	[AS (650) + COD (62)]; [AS (650) + C]; [AS (650)]; P	[AS + COD) > [AS + C); AS > P	
4	Wallenstein, 1975	Cancer (33)	DB/X	30, 60	[AS (210) + AP (150)]; [AS (210) + AP (150) + C] [×1, ×2]	(AP + AS + C) > (AS + AP) > P	1.3[B,§]
5	Wojcicki et al., 1977	Orthopaedic (72)	DB/X	100	[AP (1000) + C]; AP (1000) or AS (1000)	(AP + C) > AP; AS > P	
	Postpartum						
6	DeKornfield et al., 1962	Postpartum (198)	DB	30, 120	[AS (640)]; [AS (270) + PH (270) + SAL (240) + C]; [AS (390) + PH (360) + C]	All > P	
7	Bauer et al., 1974	Cramping (610)	DB	30, 60	[AS (454)]; [AS (227) + PH (160) + C]; [AS (227) + PH (160)] [1, ×2]	No dose response	
8	Jain et al., 1978	Moderate + severe (70)	DB	64	[AS (800) + C]; [AS (650)]	(AS + C); AS > P	[C]
9	Jain et al., 1978	Severe (70)	DB	64	[AS (800) + C]; [AS (650)]	(AS + C) > AS > P	[B]
10	Laska et al., 1983	Episiotomy/uterine cramping (373)	DB	64, 128, 198	[AP (500)]; [AP (500) + C] [×1, ×2, ×3]; P	(AP + C) > AP > P	1.9[B]
11	Laska et al., 1983	Episiotomy/uterine cramping (434)	DB	64, 128, 198	[AP (500)]; [AP (500) + C] [×1, ×2, ×3]; P	(AP + C) > AP > P	1.8 (pooled 1.7[B,¶])
12	Laska et al., 1983	Episiotomy (538)	DB	64, 128, 198	[AP (500)]; [AP (500) + C] [×1, ×2, ×3]; P	(AP + C) > AP > P	1.3
13	Rubin and Winter, 1984	Postpartum (episiotomy) (500)	DB	65	[ASA (800) + C]; [AP (648) + AS (648)]; (AP (1000)]; P	(AS + C), (AP + AS) > APAP > P	[C]
14	Jain et al., 1988	Postpartum (episiotomy) (147)	DB	100	[IBU (200) + C]; [IBU (400)]; P	(IBU + C); IBU > P	[C]
15	Sunshine et al., 1989	Postpartum (episiotomy) (302)	DB	100	[IBU (50, 100, 200)]; [IBU (100, 200) + C]; P	(IBU + C); IBU > P	1.3[B]
16	Sunshine et al., 1989	Postpartum cesarean section (185)	DB	100	[IBU (50, 100, 200)]; [IBU (100, 200) + C]; P	(IBU + C); IBU > P	1.0 (pooled 1.23[B,¶])

imately 500 mg; ibuprofen, 200 mg) is given alone or in combination with caffeine have shown statistically significant enhancements of the NSAID effect when caffeine is given in doses of 64, 100, and 130 mg (table 1).

Examination of the effects of caffeine alone have not routinely been assessed. Significantly, however, examination of the effects of single doses of caffeine has shown modest numerical increases in analgesic action compared with effects of placebo. Forbes et al. (1990) observed such changes in the percentage of patients reporting >50% pain relief after dental surgery. Winter et al. (1983) observed that caffeine (130 mg) alone resulted in a statistically significant increase in two of six pain measures, including the global assessment score, compared to placebo. In one of the only reported studies in which a complete dose-response curve was assessed for caffeine, Ward et al. (1991) observed that the drug resulted in a dose-dependent reduction in headache scores when given with acetaminophen (648 mg), as evidenced by the rank ordering in the effectiveness of the adjuvant by dose: 130 mg caffeine, 65 mg caffeine, 0 mg caffeine. Caffeine alone has been shown to have prominent effects on certain specific pain states such as associated with dural puncture (see section IV.B.2.a).

Although caffeine is considered a safe and approved additive at doses up to 200 mg given at intervals of not

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TABLE 1
Continued

Study no.	Authors†	Pain population (no.)	Study comments	Caffeine dose (mg)	Agent (doses)	Outcome	Relative potency + caffeine‡
17	Sunshine et al., 1989	Postpartum (cramping) (300)	DB	100	[IBU (50, 100, 200)]; [IBU (100, 200) + C]; P	(IBU + C); IBU > P	1.3[B]
18	Laska et al., 1984[b]	Postpartum (3010)	DB	65 × 1, ×2, ×3	[AP (500) + C], ×1, ×2, ×3; [AP (500)] ×1, ×2, ×3; P	(AP + C) > AP > P	1.37[B]
19	Laska et al., 1984[c]	Postpartum (719)	DB	65 × 1, ×2, ×4	[AS (210) + AP (210)]; [AS (210) + AP (210) + C] [×1, ×2, ×4)	(AP + AS + C) > (AP + AS) > P	1.58[B,#] (pooled 1.55[B,¶])
20	Laska et al., 1984[d]	Postpartum (488)	DB	22, ×1–×11	[AP (70) + AS (70) + C] × 1–11, [AP (70) + AS (70) + C] [×1–11], P	(AP + AS + C) > (AP + AS) > P	1.52**
	Sore throat						
21	Schachtel et al., 1991	Sore throat (207)	DB	64	[AS (800) + C]; [AS (800)]; P	(AS + C) > AS > P	[B]
	Dental pain						
22	Booy, 1972	Severe pain (210)	DB	100	[AP (1000)]; AP (1000) + C]; P	(AP + C) > AP > P	[B]
23	Winter et al., 1983	Dental surgery (164)	DB	130	[AP (1000) + C]; [AP (1000)]; C; P	(AP + C); AP > C ≥ P§·††	
24	Laska et al., 1983	3rd molar (173)	DB	128, 256	[AP (500)]; AP (500) + C] [×1, ×2]	(AP + C) > AP	‖
25	Forbes et al., 1991	3rd molar (298)	DB	100	[IBU (100, 200) + C]; [IBU (50, 100, 200)]; P	(IBU + C) > IBU ≫ P	2.9[B]
26	Forbes et al., 1990	3rd molar (350)	DB	65	[AS (650) + C]; [C]; [AS (650), 1000)]; P	(AS + C) > AS > C = P	[B,‡‡]
	Headache						
27	Currier and Westerberg, 1958	Unspecified (28)	DB	16, 32	[AS (320) + PH (160) + C]; [AS (320)]; P	AS; (AS + PH + C) > P	
28	Frey, 1961	Muscle tension (2554)	DB	30	[AS (1300)]; [AS (1300) + PH + C]; [SAL] [AS + AP + C + SAL], P§§	AS; (AS + PH + C) > P	
29	Frey, 1961	Muscle tension (150)	DB	30	[AS (1300)] [AS (1300) + PH + C]; P§§	AS; (AS + PH + C) > P	
30	Wojicki et al., 1977	Unspecified (144)	DB	100	[AP (1000) + C] AP (1000) or AS (1000)	(AP + C) > AP; AS > P	
31	Ward et al., 1991	Nonmigraine (53)	DB	65, 130	[AP (648) + C]; [C]; [AP (648)]; P	(AP + C130); C130; (AP + C65) > C65; AP; P	
32	Sechzer and Abel, 1978	Dural puncture (41)	DB	250	C, P	C > P	[B]
33	Camann et al., 1990	Dural Puncture (40)	DB	300	C; P	C > P	[B]

* Abbreviations: IND, indomethacin; AS, aspirin; AP, acetaminophen; 3rd molar, tooth extraction during dental surgery; Dural puncture, pain secondary to dural puncture and CSF loss; DB, double blind; X, crossover study; P, placebo; >, significant ($P < 0.05$). C, caffeine; COD, codeine; PH, phenacetin; SAL, salicylamide.

† a: historical interest only; b: studies 23–29 in Laska et al., 1984, pooled potency ratio; c: study 21 in Laska et al., 1984; d: study 22 in Laska et al., 1984.

‡ A: no statistical analysis can be derived; B: $P < 0.05$; caffeine + NSAID versus NSAID alone; C: effect of higher dose of NSAID + caffeine not different from effect of lower dose of NSAID alone.

§ Paradigm would require 50% difference to establish a difference between NSAID alone and combination.

‖ Bioassay data displayed negative slope, e.g., effect of high dose ≤ effect of lower dose; potency ratio not computed.

¶ Pooled estimate of potency.

Relative potency computed without the highest caffeine dose is 1.71 ($P < 0.05$).

** Relative potency computed without the highest caffeine dose is 1.68 ($P < 0.05$).

†† Caffeine alone > placebo on some pain measures ($P < 0.05$).

‡‡ Caffeine combination > effect at high dose; no statistics for potency ratio.

§§ Doses not indicated.

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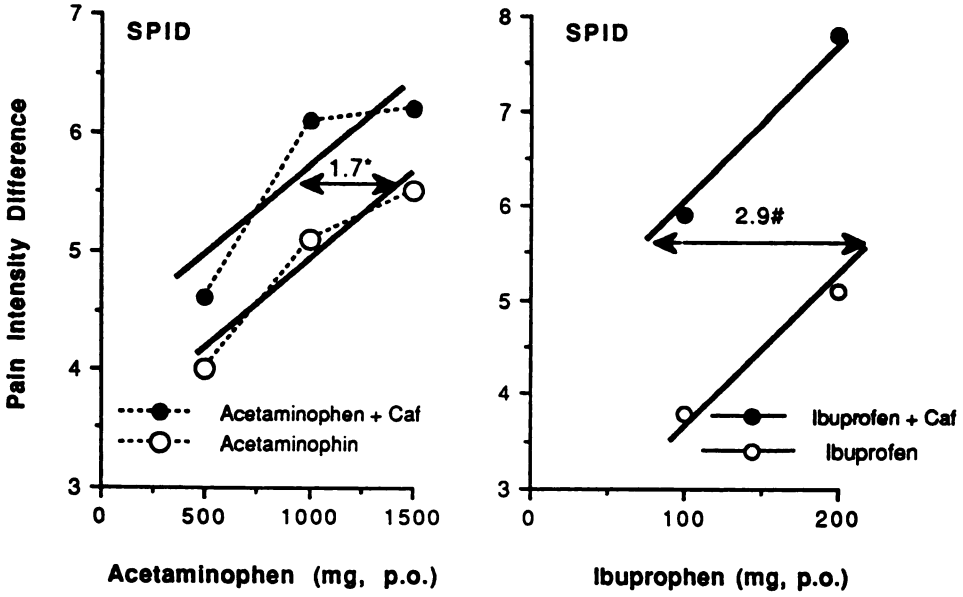

FIG. 2. Dose-response curves for the analgesic effect of oral acetaminophen alone and with caffeine (Caf) in patients with postpartum pain (left) and for ibuprofen alone and with caffeine (right) in patients after third molar extraction. The y axis is the sum of the pain intensity difference (SPID). Figures are adapted from the work of Laska et al. (1983; p. 503, table IV) and Forbes et al. (1990; p. 680, figure 3). *$P < 0.05$; #$P < 0.01$.

TABLE 2

*Pooled relative potency estimates for the analgesic action of NSAIDs alone versus the action of NSAIDs and caffeine in humans**

Drug	Combined subject population	Relative potency	95% Limits	
			Upper	Lower
Acetaminophen	2,625	1.37	1.13	1.70
Aspirin and acetaminophen	6,037	1.38	1.11	1.78
All combinations†	10,608	1.41	1.23	1.63

* Adapted from Laska et al., 1984, table 4, p. 1715.

† Overall data pool contains a variety of NSAID combinations, such as aspirin, acetaminophen, salicylamide; or groups in which comparisons were made between individuals receiving an NSAID combination (aspirin + acetaminophen) with caffeine and individuals receiving an equiactive dose of one of the NSAIDs alone (i.e., aspirin or acetaminophen).

less than 3 h (FDA Advisory Review, 1975) or in oral doses not to exceed 600 mg/24 h (Over the Counter Drugs, 1977), to our knowledge there have been no systematic studies of higher doses of caffeine carried out with submaximal concentrations of the NSAIDs. Thus, although higher doses of caffeine have been used (e.g., up to 260 mg caffeine, see study 20 in table 1), these doses have always been given in the presence of proportionately higher doses of the NSAID. This occurs because the majority of the studies were aimed at defining the efficacy of caffeine administered in a particular commercially available combination formulation. Thus, the NSAID and caffeine are administered as a fixed ratio (e.g., 1, 2, or 4 tablets are given consisting of 64 mg caffeine and 500 mg acetaminophen). There have been, in fact, few investigations in which the dose of NSAID was held constant and changes were made in the dose of caffeine.

Although there appears to be substantial evidence that caffeine can, under certain circumstances, augment the antinociceptive effects of an NSAID, the lack of caffeine dose-response curves that span the usable range of the drug in the presence of a fixed NSAID dose hinders the interpretation of the adjuvant actions of caffeine. The fixed ratio data may actually serve to underestimate the apparent adjuvant activity of caffeine. Thus, from a theoretical perspective, depending on the pain system, NSAIDs likely work by mechanisms that play a contributory, but not unique, role in the processing of nociceptive information. These agents will thus functionally display a limited intrinsic activity and a plateau in their apparent analgesic efficacy. Given the paradigms of the currently published studies, the only time high doses of caffeine are used are in those circumstances in which high doses of NSAIDs are used and the theoretical limit to the component of the pain state that may be NSAID sensitive is approached. In such studies, because of the plateau in drug effect, there may be less apparent difference between the NSAID + caffeine and NSAID group than would be predicted. In at least two sets of bioassay experiments (table 1, experiments 19 and 20), the potency ratio increased from 1.58 to 1.71 and 1.55 to 1.68, when the highest caffeine dose group was deleted from the analysis. These observations are supported by those experiments in which the greatest pain score differences for NSAID+ caffeine versus the same dose of NSAID alone was observed at concentrations of 60 to 100 mg caffeine. Thus, at the concentration of 260 mg caffeine (corresponding to 770 mg aspirin and 770 mg acetaminophen), there appears to be little effect of adding caffeine. This lack of effect may correspond to the occurrence of a plateau effect of the NSAIDs or, alternatively,

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to a nonmonotonic relationship between dose and any adjuvant activity of caffeine.

2. Test stimulus and pain state. Table 1 emphasizes that NSAID/caffeine combinations have been widely examined in a wide variety of pain states. The importance of this consideration relates to the fact that different pain states can be mediated to a different degree by different mechanisms that may be caffeine sensitive (i.e., vasomotor tone versus inflammation versus acute tissue mechanical distortion).

a. HEADACHES. For nonmigranous headaches of mixed etiology, notably those classified as muscle tension or muscle contracture headaches (Olesen and Bonica, 1990), NSAIDs as a class are widely accepted as being efficacious. The etiology of muscle tension headaches is complex. Electromyelographic studies have, in fact, suggested that long-lasting tonic contractions and local muscular tenderness may be identified in some, but not all, headache sufferers (Pikoff, 1984; Langemark and Olesen, 1985). Agents such as acetaminophen and aspirin will exert a dose-dependent reduction in the magnitude of the reported pain (table 1).

Combinations of caffeine and NSAIDs have been shown to be more efficacious than equal doses of the NSAID alone over the range of caffeine doses examined (65 to 130 mg) when given with acetaminophen alone or with acetaminophen and aspirin (table 1). The efficacy of this drug combination may reflect a potent action of caffeine by itself in this pain state. Thus, Ward et al. (1991) demonstrated that caffeine alone produced headache relief that was superior to acetaminophen (648 mg) alone and, although numerically less, was not statistically different from the relief obtained with acetaminophen (648 mg). Because of this powerful effect when given alone, it is surprising that more studies have not been performed with caffeine-alone groups, as used by Ward and colleagues.

In addition to muscle tension-type headaches, headaches secondary to dural puncture (table 1; Sechzer and Abel, 1978; Jarvis et al., 1986; Aguilera et al., 1988; Ford et al., 1989; Marcelis and Silberstein, 1990; Fernandez, 1990; Camann et al., 1990) or to low CSF pressures (Marcelis and Silberstein, 1990) are prominently diminished by caffeine alone in doses of 250 to 300 mg. The mechanisms by which i.t. hypotension results in headache is unknown. Two hypotheses currently exist: (*a*) distention of the brain and meninges and (*b*) dilation of intracranial blood vessels (Miyakawa et al., 1977; Hattingh and McCalden, 1978; Sechzer, 1979; Fernandez, 1990). It has been suggested that caffeine (and other methylxanthines) may relieve these symptoms by increasing cerebrovascular tone and decreasing cerebrovascular volume and flow (Denker, 1931; Moyer et al., 1952; Shenkin and Novoack, 1954; Dodd et al., 1989). Significantly, oral doses of 250 mg caffeine were shown to induce cerebral vasoconstriction within 30 min of administration, and this effect lasted for at least 90 min. Alternately, abstinence from caffeine for a period of 24 h by patients with an average consumption of six cups of coffee per day (approximately 900 mg/day) resulted in prominent increases in frontal pole blood flow (Mathew et al., 1983; Mathew and Wilson, 1985). Importantly, as will be discussed below, abstinence from caffeine by individuals who consume large quantities of caffeine can induce significant headaches (see section VIII.C).

b. POSTPARTUM PAIN. Postpartum pain states typically are divided into those arising from simple vaginal delivery, episiotomy, and/or uterine cramping/post-Caesarean section, in order of increasing pain intensity. NSAIDs produce a dose-dependent suppression of pain reports. In 17 studies, caffeine, over a range of 65 to 100 mg, numerically increased the potency of acetaminophen and ibuprofen relative to the NSAID alone, and this difference reached statistical significance in five of the 17 studies (table 1).

c. DENTAL SURGERY PAIN. Because of the local injury to the gum and the ensuing inflammatory response, dental surgery provides an excellent model of inflammatory pain. Pain reports generated in such an experimental state have been shown to be depressed in a dose-dependent fashion by NSAIDs. As indicated in table 1, caffeine will augment the effects of NSAIDs.

d. POSTOPERATIVE PAIN. Postoperative nondental pain represents an important area that has been poorly examined. In part, it might be presumed that NSAIDs are weak analgesics and that the use of such agents in acute postoperative pain states is necessarily inadequate. In addition, there has been the concern that such treatment might augment bleeding times. Results of a large number of studies have, however, emphasized that NSAIDs, such as aspirin and acetaminophen (table 1), ketoralac (Yee et al., 1986; O'Hara et al., 1987), ketoprophen (Sunshine and Olson, 1988), indomethacin (McGlew et al., 1991), among others, can produce a prominent reduction in postoperative pain following significant surgical interventions, such as joint replacement or laparotomy. The interaction of caffeine with other NSAIDs in strong pain states has not been evaluated. As noted above, the contributory effect of caffeine appears to be augmented as the intensity of the pain state is increased.

3. Stimulus intensity. In addition to the origin of the stimulus, an important variable is the magnitude of the stimulus. Laska et al. (1983), in an extensive bioassay study, separated postpartum women into categories of simple episiotomy versus episiotomy and uterine cramping. Over a range of acetaminophen doses (500 to 1500 mg) given alone or with caffeine (64 to 192 mg), the relative potency in the presence of caffeine was 1.6 versus 2.3, respectively. This suggests that in the presence of the more intense stimulus, caffeine appeared to exert a greater adjuvant effect. Similar results were reported by Jain et al. (1978), with postpartum pain and by Booy

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(1972) and Forbes et al. (1990) with post-dental surgery pain. In most of these instances, the reported effectiveness of the NSAID alone was diminished as the pain intensity was perceived to be more severe. Thus, post hoc analysis of the data as a function of reported pain prior to medication revealed that the addition of caffeine to the NSAID dose formulation served to achieve the same degree of pain relief (satisfaction) in those patients reporting severe pain as the relief reported by the patients with less intense pain. In short, as the reported intensity of the pain message increases, caffeine appears to become more effective as an adjuvant. It is interesting to note that, in the study on dental pain by Winter et al. (1983), the combination of acetaminophen (1000 mg) and caffeine (135 mg) was not different from acetaminophen alone, but of the patients constituting the combination group, five of 40 had severe pain, whereas in the acetaminophen group alone 13 of 41 had severe pain. Several explanations may account for this observation. (*a*) More intense pain states (i.e., more tissue damage) may reflect the inclusion of systems that are mediated by caffeine-sensitive mechanisms (e.g., release of active factors that stimulate nerve endings). (*b*) Increasing pain intensity can result in changes in emotional perspective that augment the perceived pain state and may be ameliorated by the psychostimulant aspects of caffeine's actions. (*c*) Measurement of the intrinsic analgesic activity of a drug requires that the magnitude of the pain exceed the possible analgesic action of the agent (and its adjuvant). Thus, if the magnitude of pain is limited, above a certain level of analgesia, higher doses or the addition of an adjuvant will erroneously appear to make no additional difference (i.e., have no effect). Under this condition, more intense pain states will increase the apparent plateau of drug effect, otherwise observed at the lower dose in the lesser pain state. Under these conditions, elevated pain states may reveal the activity of the agent (i.e., NSAID) and its adjuvant (caffeine) acting jointly.

To address these issues, systematic caffeine dose-response curves need to be obtained both alone and in the presence of fixed, submaximally effective doses of NSAIDs in different pain states.

C. Summary

NSAIDs have been shown to produce a significant, dose-dependent, amelioration of the pain state in a variety of clinical situations, including postoperative dental pain and postoperative pain such as episiotomy, cramping, and headache. The addition of caffeine, in a dose range as low as 65 and 130 mg, will augment the antinociceptive effects of several NSAIDs, including aspirin, acetaminophen, and ibuprofen. This augmentative effect of caffeine appears most prominent at the lower doses of NSAIDs and in the presence of a more intense stimulus. The more prominent activity of caffeine with more intense pain states may reflect (*a*) the role of a plateau effect in the measurement or (*b*) the involvement, with higher intensity stimuli, of mechanisms initiating or facilitating the pain message that are directly sensitive to caffeine. Significantly, although there are few data to define the antinociceptive effects of caffeine alone in these various human pain states, several studies have shown that caffeine may exert at least a modest antinociceptive effect on its own.

V. Analgesic and Adjuvant Action of Caffeine in Nonhumans

A. Nociceptive Response Paradigms

A variety of different tests have been developed to determine the antinociceptive activity of drugs in animals for the multiple purposes of drug screening and development, predicting clinical activity, and examining central and peripheral mechanisms of drug action. Some tests involve acute noxious stimulation (thermal: tail flick, tail immersion, hot plate; pressure: paw pressure, tail pressure, tail pinch; electrical stimulation tests), and others involve continuous stimulation (chemically induced writhing, inflamed paw, formalin tests) or neurogenic stimulation (sciatic ligature) (Taber, 1974; Franklin and Abbott, 1989; Bennett and Xie, 1988). Opioids are effective throughout this spectrum of tests (albeit with differing efficacy for different classes of opioid-like drugs), but NSAIDs show a more limited spectrum of activity, with continuous stimulation and inflammation being required to demonstrate activity (Taber, 1974; Franklin and Abbott, 1989).

In a number of studies, antinociceptive effects of caffeine alone and in combination with nonopioid and opioid analgesic drugs have been examined. The rationale has differed in these studies, as possible adjuvant properties of caffeine were examined or caffeine was used as an adenosine receptor antagonist or phosphodiesterase inhibitor to examine aspects of mechanisms of drug action (section III). Because theophylline shares these pharmacological actions with caffeine, and has a comparable potency, effects of theophylline and aminophylline, its ethylenediamine salt, also will be considered here.

Results have varied, depending on species, dose, route of administration, and antinociceptive test used. In view of the multiple pharmacological actions of caffeine produced at different tissue concentrations, it is not surprising that results are varied over a range of doses. Even when the same pharmacological action is considered, such as adenosine receptor antagonism, effects of methylxanthines may be different depending on whether a peripheral or a central site of action is involved. Thus, peripheral administration of adenosine produces pronociceptive effects (section VII.B), whereas central administration of adenosine produces antinociception (section VIII.A.1). It is, therefore, essential to consider the route

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of administration of the methylxanthine when interpreting results. When administered systemically, methylxanthines have the potential to act at both peripheral and central sites, perhaps to opposing effect. Only when the drug is delivered to discrete sites, such as to the spinal cord by i.t. injection or to supraspinal sites by i.c.v. or intracranial injection, can individual components of action be considered separately. Although intradermal administration to the paw potentially may elicit a peripheral action, it is important to perform the appropriate control experiments (e.g., contralateral injection or systemic injection of the same dose) to ensure that the effect is not due to systemic absorption of the drug. Finally, the nature of the test used, i.e., acute stimulation versus inflammatory test, may be critical because adenosine appears to play a significant role in inflammation (section VII) and the respective roles of peripheral and central actions of adenosine, and consequently methylxanthines, may differ in these different types of tests.

B. Effects of Caffeine on Nociceptive Thresholds

Systemic administration of caffeine to rats and mice at lower doses (10 to 50 mg/kg) generally has no intrinsic antinociceptive effect as determined by a variety of nociceptive tests, including (*a*) acute thermal stimulation tests: tail flick and tail immersion tests (15 mg/kg, Mantegazza et al., 1984; 40 mg/kg, Ahlijanian and Takemori, 1985; 100 mg/kg, Misra et al., 1985; 10 and 50 mg/kg, Malec and Michalska, 1988), hot plate test (50 mg/kg, Oliverio et al., 1983; 10 and 50 mg/kg, Malec and Michalska, 1988; up to 200 mg/kg, Fialip et al., 1989; 15 mg/kg, Contreras et al., 1990), (*b*) chemical inflammation: phenylbenzoquinone writhing test (≤200 mg/kg, Fialip et al., 1989), and (*c*) mechanical pressure: quantal tail pressure/tail pinch tests (≤100 mg/kg, Person et al., 1985).

In contrast, in higher doses (75 to 100 mg/kg) caffeine has been observed to produce antinociception in acute stimulation tests, although some investigators, as noted above, did not observe such activity. Caffeine alone exerted a significant antinociceptive effect in the (*a*) tail immersion test (100 mg/kg, Person et al., 1985; 75 and 100 mg/kg, Malec and Michalska, 1988), (*b*) hot plate test (75 and 100 mg/kg, Malec and Michalska, 1988), (*c*) graded tail pressure test (30 and 100 mg/kg, Person et al., 1985), and (*d*) inflammatory tests (yeast inflamed hindpaw) (50 and 100 mg/kg, Siegers, 1973; 4.5 mg/kg, Seegers et al., 1981) (but not carrageenan-induced inflammatory response, Vinegar et al., 1976).

Other methylxanthines appear to possess a similar profile of activity. Thus, at lower doses, systemic administration of theophylline or aminophylline (10 and 25 mg/kg) is without intrinsic effect in the tail flick or immersion and hot plate tests (Jurna, 1981; Malec and Michalska, 1988), whereas higher doses of theophylline (50 and 100 mg/kg) produce antinociception in the hot plate test (Malec and Michalska, 1988).

The vocalization test in rats appears unique in that systemic administration of both caffeine and theophylline (25 to 100 mg/kg) produces a reduction in motor, vocalization, and vocalization after discharge thresholds (Paalzow and Paalzow, 1973; Person et al., 1985).

The intrinsic antinociceptive action of caffeine may involve peripheral (e.g., antagonism of the action of adenosine at peripheral nerve endings, section VII) as well as central (e.g., activation of central noradrenergic systems, section VIII) components of action.

In contrast to systemic administration, the spinal or i.t. application of methylxanthines (aminophylline and the more potent adenosine receptor antagonist, 8-phenyltheophylline) produces hyperalgesia or a shortening in latency in the tail flick test in rats, provided the stimulus intensity is mild (Jurna, 1984; Sawynok et al., 1986). Such hyperalgesia has not been observed in mice (DeLander and Hopkins, 1986). The occurrence of hyperalgesia has been interpreted as reflecting antagonism of tonic activity mediated by adenosine within the spinal cord.

C. Caffeine Interactions with Nonopioid Analgesic Drugs

When caffeine has been administered in combination with NSAIDs, it has been in the context of examining possible adjuvant effects, and both drugs have been administered systemically to mimic the human context. There are limited data for the effects of these agents on noninflammatory tests because of the relative insensitivity of these tests to NSAIDs. However, caffeine has been reported to inhibit the modest antinociceptive activity of acetaminophen plus aspirin (tail immersion test, 10 mg/kg, Grotto et al., 1965) or not to alter the activity of dipyrone in the hot plate test (40 and 200 mg/kg, Fialip et al., 1989). In contrast, in inflammatory models such as the phenylbenzoquinone writhing test, where dipyrone is much more potent, caffeine enhanced the activity of dipyrone (5 mg/kg, Fialip et al., 1989). In the inflamed hind paw test in which NSAIDs show consistent activity, caffeine (50 to 100 mg/kg) augmented the duration, but not the degree, of antinociception produced by oral acetaminophen. When the acetaminophen was administered s.c., however, there was an augmentation in both the peak effect and duration of action (Siegers, 1973). The lack of increase in peak action following oral administration may have been because the caffeine was evaluated against an optimal dose of acetaminophen (200 mg/kg); increasing the dose further resulted in a diminished effect (Siegers, 1973). The lowest dose of caffeine (10 mg/kg) reduced plasma levels of, and antinociception by, acetaminophen. Because the higher doses of caffeine also reduced plasma levels, it is likely that an even greater augmentation of effect occurred at these higher doses. Other investigators have observed that caffeine aug-

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ments antinociception by aspirin in the carrageenan inflamed paw test (potentiation, Vinegar et al., 1976) and of phenacetin, acetaminophen, and aspirin in the yeast inflamed hindpaw test (additive, Seegers et al., 1981). Augmentation of the action of NSAIDS may involve both pharmacodynamic aspects (e.g., antagonism of adenosine released endogenously at peripheral nerve endings under conditions of inflammation, section VII), although pharmacokinetic mechanisms also may contribute to such interactions (section II.F).

D. Caffeine Interactions with Opioid Analgesics

Caffeine and other methylxanthines have generally been given with opioids as a means of examining mechanisms by which opioids act (e.g., role of cyclic AMP or adenosine) and, in this context, have been administered both systemically and locally into the spinal cord. Methylxanthines have not usually been given by i.c.v. administration, but in view of clear supraspinal actions of opioids (reviewed by Yaksh et al., 1988), this may be required to examine separately a potential supraspinal component of action.

When both morphine and methylxanthines are given systemically, both caffeine and theophylline can augment the effects of morphine, as measured by a number of nociceptive end points, including (*a*) tail compression and tail pinch tests (caffeine 30 mg/kg, Person et al., 1985; 100 mg/kg, Misra et al., 1985), (*b*) tail immersion and hot plate tests (caffeine 25 to 100 mg/kg and theophylline 50 and 100 mg/kg, Malec and Michalska, 1988), (*c*) mouse tail flick test (theophylline 100 mg/kg 1 h before, Ho et al., 1973), and (*d*) vocalization test (theophylline 50 mg/kg, Paalzow, 1979).

Caffeine 10 mg/kg also enhances the ability of morphine to suppress the cardiac acceleration response following noxious stimulation (Kissin and Jebeles, 1984).

In contrast to the enhancement of antinociception, there are also reports that caffeine (40 mg/kg, mouse tail flick, Ahlijanian and Takemori, 1985; 10 mg/kg, mouse tail immersion and hot plate tests, Malec and Michalska, 1988), theophylline (100 mg/kg, 4 to 24 h before, mouse tail flick test, Ho et al., 1973; theophylline 10 and 25 mg/kg, mouse hot plate test, Malec and Michalska, 1988), and aminophylline (25 mg/kg, rat tail flick test, Jurna, 1984) inhibit the antinociceptive action of morphine.

Such reports as described above may appear contradictory, but there is a general pattern whereby inhibition is observed with lower doses (10 to 40 mg/kg or at longer pretreatment times with 100 mg/kg) and augmentation at higher doses (25 to 100 mg/kg) of methylxanthines. Such a biphasic action might explain why some intermediate doses do not alter the action of morphine (caffeine 50 mg/kg, Oliverio et al., 1983), although the lack of effect of a low dose of theophylline on morphine (15 mg/kg, mouse hot plate test, Contreras et al., 1972) also has been noted. Potentiation of antinociception may reflect blockade of a peripheral pronociceptive action of adenosine (section VII), whereas antagonism of antinociception may reflect an interaction between adenosine and morphine in the spinal cord (section VIII.A).

When morphine is administered spinally, and its actions are confined to a spinal site, methylxanthines uniformly inhibit the action of morphine. This has been demonstrated for systemic aminophylline (rat tail flick test, Jurna, 1984) and for i.t. caffeine, theophylline, and 8-phenyltheophylline (DeLander and Hopkins, 1986; Sweeney et al., 1987). Because spinal administration of adenosine agonists has been reported to produce antinociception according to results of a variety of tests (section VIII.A.1), such observations have been interpreted as suggesting that morphine releases adenosine from the spinal cord. Accordingly, morphine has been shown to release adenosine from the spinal cord both in vitro and in vivo (Sweeney et al., 1987; 1989). This adenosine originates from capsaicin-sensitive afferent terminals in the spinal cord (Sweeney et al., 1989).

Interestingly, when morphine is administered supraspinally, spinal release of adenosine also may contribute to supraspinal antinociception because spinal methylxanthines reduce antinociception by i.c.v. morphine (tail flick and hot plate tests, DeLander and Hopkins, 1986; Sweeney et al., 1991; substance P and NMDA scratching behavior, DeLander and Wahl, 1989) and morphine administered into the periaqueductal gray (hot plate test, Sawynok et al., 1991). In the rat, at higher doses, spinal theophylline potentiates the action of i.c.v. morphine (Sweeney et al., 1991), indicating that multiple actions of methylxanthines may manifest at a single site of action.

E. Summary

In animal models of nociception, caffeine produces complex effects on pain thresholds and on antinociception by opioid and nonopioid analgesic agents. Such actions are dependent of the dose and route of administration of caffeine, as well as on the analgesic agent being examined, because the different classes of agents act by quite distinct mechanisms. Systemic administration of caffeine produces intrinsic antinociceptive effects in some inflammatory and noninflammatory tests, although this was not noted in all studies in which the same test was used.

A lowering of nociceptive threshold (hyperalgesia) occurs following spinal administration of methylxanthines. Caffeine augments antinociception by NSAIDs in some studies, although kinetic variables and study design (e.g., lack of complete dose-response curves) serve to confound the interpretation of results. Enhancement of antinociception in inflammatory tests does not appear to be due to a direct anti-inflammatory action of caffeine, because it occurs at much lower doses.

Both intrinsic antinociception and augmentation of

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the action of NSAIDs may reflect blockade of peripheral pronociceptive actions of adenosine. Methylxanthines produce biphasic effects on antinociception by systemic opioids, generally inhibiting it at lower doses (10 to 30 mg/kg) but augmenting it at higher doses (50 to 100 mg/kg). Spinal administration of methylxanthines antagonizes both spinal and supraspinal antinociception by opioids by antagonizing the action of adenosine released from the spinal cord by opioids. Such observations emphasize that the action of a systemically administered agent having central as well as peripheral actions (as does caffeine) will reflect the net outcome of parallel and, perhaps, physiologically antagonistic events.

VI. Psychomotor Effects of Caffeine

A. Psychomotor Effects in Humans

Caffeine exerts a variety of effects on human behavior. Because of its observed effects, it has been generally classified as a psychomotor stimulant (Rall, 1985). Such actions might conceivably lead to changes in the manner by which humans perceive the pain state.

1. Effects on electroencephalogram. Bruce et al. (1986) observed that, in humans, caffeine (250 and 500 mg, p.o.), giving rise to peak plasma concentrations of approximately 6 and 12 μg/ml, respectively, increased arousal, and there was a correlated decrease in time spent in a slow wave (theta) electroencephalogram state during a 5-h period.

2. Vigilance. Hollingsworth (1912), in one of the earliest systematic studies, emphasized the stimulant effects of caffeine on motor and mental activities, an observation that has been largely confirmed during the last half century (Weiss and Laties, 1962; Dews, 1982). In humans, caffeine exerts an augmenting effect on vigilance and attention and prevents the decrement in performance and information processing that occurs during a fatigued state or in an environment lacking novelty. This augmentation is reflected by improvements in subject reports of alertness (Lieberman et al., 1987a; Uematsu et al., 1987), improved reactions times (Lieberman et al., 1987), and improved attention span (Ghoneim et al., 1986; Frewer and Lader, 1991). A consistent factor in the large number of studies thus far reported appears to be that the improvements made by caffeine, as compared to placebo, are observed in those test states in which significant fatigue or a stressful workload is impressed on the test paradigm.

Investigations of systematic effects have indicated that in doses of 65 to 500 mg caffeine, there are apparent improvements in psychomotor performance and in self-reported alertness (Clubley et al., 1979; File et al., 1982; Lieberman et al., 1987a). In repetitive or extended interval tasks, caffeine in doses of 32 to 256 mg has been shown to improve vigilance and multiple-choice reaction time tests (Lieberman et al., 1987a,b). With regard to complex mental function measures, the literature is controversial. It can be intuitively appreciated that performance may be related to changes in vigilance, boredom, and complexity of the test. As such, it is not surprising that nonmonotonic dose-response curves may be seen with high caffeine doses, resulting in a performance decrement (Anderson and Revelle, 1983; Cattell, 1930; Gilliland and Nelson, 1939; Loke 1988; Foreman et al., 1989), emphasizing that certain levels of arousal may lead to optimal test performance.

3. Well-being. An important aspect of caffeine utilization relates to the desirability to the subject of the effects produced by the agent. In patients with headache, caffeine has been reported to produce positive improvements in mood (Ward et al., 1991). More important, such positive changes have been reported in humans not in a pain state. Thus, using self-reporting mood questionnaires, such as the Profile of Mood States scale or the MBG (morphine-benzedrine group) scale of the Addiction Research Center Inventory, several investigators have reported that caffeine in doses of 64 to 130 mg will significantly increase euphoria and vigor and diminish fatigue and depression scales in normal subjects (Lieberman et al., 1987a; Stern et al., 1989; Griffiths et al., 1990) and evoke positive mood changes, defined in terms of a sense of well-being (Goldstein et al., 1965a,b; File et al., 1982), pleasantness (Svensson et al., 1980), and contentedness (Bruce et al., 1986).

It should be stressed that the positive effects of caffeine on mood may vary because of several factors. First, there is little question that humans are able to positively discriminate low doses of caffeine. Griffiths et al. (1990), in an extended and well-defined study, examined the ability of seven trained subjects to discriminate daily between capsules ingested sequentially at 1- to 2-h intervals containing either placebo or caffeine. In these studies, it was found that subjects could reliably discriminate drug from placebo at doses of 5.6 to 30 mg. Nevertheless, the psychological component of the actions of a mild stimulant, such as caffeine, is strongly dependent on patient or subject expectations (Christensen et al., 1990). Second, failure to detect subtle mood changes induced by psychoactive drugs with specific verbal descriptors may also reflect on the measuring instrument. For example, failure to establish concrete descriptors for positive mood changes induced by cocaine has also been reported (cf. Marbach and Wallenstein, 1988). Third, the positive aspects of caffeine appear to follow a biphasic dose-effect relationship. Thus, in doses up to 100 to 200 mg, there is a significant positive effect. On the other hand, at much higher doses (400 mg), the population response to caffeine appears to be dysphoric and anxiogenic (section VI.A.5). These three variables, and an anticipated variation in population responding, may account for some of the variability observed in the reported data concerning the perceptual and psychomotor effects of caffeine.

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4. Reinforcing properties. Systematic studies of the reinforcing properties of caffeine in humans are few. In volunteer populations of subjects displaying low to moderate dietary caffeine consumption, high doses (300 to 600 mg) of caffeine in an experimental situation have been reported to be aversive (Stern et al., 1989; Griffiths and Woodson, 1988a,b). At lower doses (100 to 200 mg) there is little (Griffiths and Woodson, 1988a,b) or no incidence of self-administration (Stern et al., 1989) as compared to placebo. It should be noted that chronic caffeine consumption leads to a condition in which caffeine abstinence for intervals of 12 to 24 h results in a withdrawal state characterized by irritability, insomnia, muscle twitching, and, most frequently, headaches (White et al., 1980; Greden et al., 1980; Stringer and Watson, 1987; Smith, 1987; Van Dusseldorp and Katan, 1990; for review, see Griffiths and Woodson, 1988c). Reversal of such aversive states would serve as a reinforcer for self-administration in subjects that were deprived of caffeine (as in the study reported by Griffiths and Woodson, 1988b).

5. Anxiogenic properties. Caffeine in the range of 240 to 720 mg (10 mg/kg) has been shown to result in significantly greater signs and reports of anxiety and induced panic attacks at the highest doses in normal adult volunteers (Uhde et al, 1984; Charney et al., 1984; Griffiths and Woodson, 1988a) and augmented attacks in patients suffering from panic disorders (Charney et al., 1985). The clinical syndrome associated with chronic caffeine exposure (caffeinism) has been described as indistinguishable from that of various anxiety states (Powers, 1925; Greden, 1974).

B. Psychomotor Effects in Nonhumans

1. Stimulant properties. a. BEHAVIORAL EFFECTS. Caffeine is a behavioral stimulant and shares some functional characteristics with other stimulants such as amphetamine and methylphenidate. In rats and mice, caffeine (3 to 30 mg/kg) produces a dose-related increase in motor activity (Thithapandha et al., 1972; Holtzman, 1983; Finn and Holtzman, 1986; Logan et al., 1986; Buckholtz and Middaugh, 1987) that either attains a plateau level of activity (Holtzman, 1983; Finn and Holtzman, 1986) or shows a reduced activity at higher doses (DeAngelis et al., 1982; Finn and Holtzman, 1987; Buckholtz and Middaugh, 1987).

In drug discrimination studies, rats trained while receiving low (10 mg/kg), but not high (30 mg/kg), doses of caffeine show generalization to amphetamines and methylphenidate (Holloway et al., 1985; Holtzman, 1987). Despite this functional resemblance and some generalization to other stimulants, caffeine has properties that clearly distinguish it from other well-known stimulants. Caffeine (Atkinson and Enslen, 1976; Collins et al., 1984; Yanagita, 1970; Hoffmeister and Wuttke, 1973), unlike amphetamine (Pickens and Harris, 1968; Balster and Schuster, 1973), will not readily support self-administration behavior in rats or primates. When current thresholds required to support intracranial self-stimulation in rats are examined, caffeine (Mumford et al., 1988; Mumford and Holtzman, 1990), in contrast to amphetamine (Schaefer and Holtzman, 1979), will result in a dose-dependent increase in threshold currents (3 to 60 mg/kg) and a reduction in response rate (30 to 60 mg/kg). Rats chronically exposed to caffeine will show a progressive rightward shift and a reduced maximum in the dose-response curve for the motor stimulant effects of caffeine carried out after chronic caffeine exposure. Similar right shifts are observed in the dose-response curves for the motor stimulant properties of theophylline (another methylxanthine) but not the nonxanthines, methylphenidate, amphetamine, and cocaine (Holtzman, 1983; Finn and Holtzman, 1987). The latter observation emphasizes a lack of cross-tolerance between methylxanthine and nonmethylxanthine stimulants.

b. PHARMACOLOGY OF STIMULANT PROPERTIES OF CAFFEINE. A number of methylxanthines share the behavioral stimulant properties of caffeine. Systemic administration of analogs of adenosine produces a dose-dependent reduction in motor activity that is blocked by methylxanthines (Vapaatalo et al., 1975; Snyder et al., 1981; Dunwiddie and Worth, 1982). In general, the ability of methylxanthines to induce motor stimulation correlates with their order of potency as adenosine receptor antagonists (Snyder et al., 1981; Katims et al., 1983). This relationship no longer holds as methylxanthines become more potent as phosphodiesterase inhibitors (Choi et al., 1988), reflecting the behavioral depression characteristic of nonxanthine phosphodiesterase inhibitors (Wachtel, 1982). Accordingly, 3-isobutyl-1-methylxanthine, which is a potent xanthine phosphodiesterase inhibitor, produces only depression of motor activity over a range of doses (Snyder et al., 1981; Katims et al., 1983). The plateau effect or reduction in locomotor stimulation seen with high doses of caffeine (Holtzman, 1983; DeAngelis et al., 1982; Finn and Holtzman, 1986, 1987; Buckholtz and Middaugh, 1987) may well be due to phosphodiesterase inhibition at such higher doses.

The pharmacology of self-administered caffeine is similar, because such actions of caffeine are mimicked by other methylxanthines with a potency that parallels the activity of these agents as adenosine receptor antagonists (Mumford and Holtzman, 1990). The reduction in response rate seen at higher doses of methylxanthines was observed with nonxanthine phosphodiesterase inhibitors (Mumford and Holtzman, 1990), indicating that the pattern observed with locomotor stimulation is applicable to another stimulation paradigm.

Chronic exposure to caffeine results in a dramatic reduction in the motor stimulant effects of caffeine (Ahlijanian and Takemori, 1986b; Holtzman, 1987; Finn and Holtzman, 1986, 1987). Although chronic exposure to

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caffeine or theophylline results in an increase in the number of adenosine receptors (usually 10 to 30%) (Fredholm, 1982; Boulenger et al., 1983; Chou et al., 1985; Hawkins et al., 1988), this mechanism does not appear to underlie tolerance to caffeine. Thus, adenosine analogs still inhibit locomotor activity following chronic caffeine pretreatment (albeit with less potency, probably due to antagonism by residual caffeine), but the potency of caffeine in antagonizing this action in control and tolerant animals is the same (Holtzman et al., 1991). There is one report of chronic caffeine exposure increasing the ability of *R*-phenylisopropyl adenosine to depress locomotor activity and decreasing the effectiveness of caffeine as an antagonist, but this was accompanied by a dramatic increase in receptor number (double) not seen in other studies (Ahlijanian and Takemori, 1986b). The mechanistic basis of caffeine tolerance may reside in other forms of adaptation, such as alterations in G-protein levels and coupling to adenosine receptors (Ramkumar et al., 1988; Fastbom and Fredholm, 1990).

c. CENTRAL SYSTEMS MEDIATING PSYCHOMOTOR EFFECTS OF CAFFEINE. Methylxanthines enhance the turnover of NA in brain (Berkowitz et al., 1970; Waldeck, 1971; Corrodi et al., 1972; Goldberg et al., 1982; Hadfield and Milio, 1989), and the role of NA systems in psychomotor effects of caffeine has been addressed directly. In rats trained to discriminate caffeine, discriminative effects are blocked by the α-adrenergic antagonist, phentolamine, while the α_1-adrenergic agonist, ST-587, generalizes to caffeine (Holtzman, 1986). Such observations implicate adrenergic mechanisms in drug discrimination responses. Pretreatment with reserpine and α-methyl-*p*-tyrosine, which deplete brain catecholamines, reduces stimulation of motor activity by caffeine (White et al., 1978; Finn et al., 1990).

A variety of studies have implicated the mesolimbic dopamine system in psychomotor stimulation by centrally active agents (Swerdlow et al., 1986). However, although lesions to the nucleus accumbens induced by 6-hydroxydopamine inhibit motor stimulation by amphetamine, cocaine, and methylphenidate (Kelly et al., 1975; Kelly and Iversen, 1976), such lesions do not alter the effect of caffeine (Joyce and Koob, 1981). Thus, although catecholamine systems are implicated in the stimulant action of caffeine, the neurotransmitter (NA versus dopamine) and specific pathways involved remain to be determined.

2. *Anxiogenic properties of caffeine.* In animal studies, caffeine produces a dose-dependent increase in behavioral indices of anxiety (File and Hyde, 1979; File et al., 1988). Adenosine agonists do not antagonize the anxiogenic effects of caffeine. Although caffeine has been shown to bind to the benzodiazepine site (section III.F), flumazenil (a benzodiazepine antagonist) was unable to alter the anxiogenic actions of caffeine (Baldwin and File, 1989).

C. Summary

In humans, caffeine enhances psychomotor performance by increasing vigilance, alertness, and attention span. The augmenting effect of caffeine on performance and mood state appears evident particularly under conditions of fatigue, stress, and elevated workload. Caffeine also produces positive effects on mood, although these may be difficult to quantify with current psychometric instruments. At higher doses, effects on psychomotor performance and mood may be detrimental. Tolerance to caffeine occurs following chronic ingestion, and effects of caffeine in tolerant individuals differ from those in other subjects. Chronic ingestion of high doses of caffeine (caffeinism) produces a syndrome indistinguishable from clinically defined anxiety states.

In animals, caffeine stimulates psychomotor activity and performance at low doses, but at higher doses, a plateau effect or reduced effect is observed. Stimulation of psychomotor activity is believed to be due to antagonism of central adenosine receptors, whereas the inhibition seen at higher doses may be due to phosphodiesterase inhibition. Chronic exposure to caffeine produces tolerance to psychomotor actions; this does not appear to be due to adenosine receptor upregulation. Central NA pathways (but not the mesolimbic dopamine pathway, as for other stimulants) appears to be involved in psychomotor stimulation by caffeine.

VII. Peripheral Mechanisms of Caffeine Interactions with Nociceptive Processing

As will be reviewed below, certain physiological, biochemical, or immunological events may result in the formation of pharmacologically active factors that can evoke or facilitate activity in specific populations of small sensory afferents. Interventions that alter the formation of those active factors can block the initiation of the pain state or prevent its augmentation. As an example, in the context of the present review, methylxanthines, in general, and caffeine, in particular, will be shown to interact with the effects of products, such as adenosine, released secondary to injury which can evoke activity in small primary afferents.

A. Chemical Mediators in Peripheral Nociceptive Transduction

Under normal circumstances, high threshold physical stimuli of a mechanical or thermal nature will activate small afferents that encode nociceptive information. In addition to physical stimuli, however, the vast majority of the small, high threshold afferents will also respond directly to a variety of chemical and pharmacological stimuli. For the C-fibers, notably those classified as polymodal nociceptors, powerful increases in activity can be generated by a number of agents, some of which are thought to act on specific receptors located on the free

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nerve ending. Several such intermediaries include the following.

1. Histamine. Histamine (granules of mast cells, basophils, and platelets) and serotonin (mast cells and platelets) are released to stimulate free nerve endings and evoke vasomotor changes (Lagunoff et al., 1983; Van Houtte, 1983; Martin et al., 1987; Mizumura et al., 1991).

2. Lipidic acids. Lipidic acids, which are synthesized by the action of lipoxygenase or cyclooxygenase (prostanoids) on cell membrane-derived arachidonic acid following the activation of phospholipase A (Wolfe, 1982), can cause sensitization of free nerve endings and increase capillary permeability (Staszewska-Barczak et al., 1976; Martin et al., 1987; Mizumura et al., 1991).

3. Kinins. A variety of kinins, notably, bradykinin, are synthesized by a cascade that is triggered when factor XII is activated by such agents as kallikrein and trypsin; these kinins are powerful activators of free nerve endings (Griesbacher and Lembeck, 1987; Lang et al., 1990). Cytokines, such as interleukins, are released as a function of immune reactivity, and these agents have been shown to induce a hypersensitivity (Ferreira et al., 1988; Schweizer et al., 1988; Martin and Resch, 1988).

4. Primary afferent peptides. Primary afferent peptides, such as calcitonin gene-related peptide and substance P, released from the peripheral terminals of C-fibers by antidromic nerve stimulation produce local cutaneous vasodilation, plasma extravasation, and stimulation of inflammatory cells to evoke the release of their granular products in the region of tissue (skin, visceral organs, lung, etc.) innervated by the stimulated sensory nerve (Lembeck et al., 1976; Lundberg et al., 1985; Bill et al., 1979; Brodin et al., 1981; Yaksh, 1988).

5. Purines. Purines, notably adenosine, may be released by ischemic and injured tissue and subsequently may activate free nerve endings (see below).

It is important to note that these products, such as bradykinin (Thomas and West, 1974), 5-hydroxytryptamine (Johannson, 1985), histamine (Gryglewski and Korbut, 1976), and adenosine (see below), will arise secondary to the intracellular products released by tissue damage, from plasma secondary to increased vascular permeability, and from inflammatory cells which, themselves, are stimulated by products in the extracellular milieu and are thus available to interact with peripheral nerve terminals.

It is now appreciated that these products, which are natural sequelae to tissue injury, play a significant role in evoking the postinjury pain state in two ways: (*a*) by directly activating free nerve endings (see above; Handwerker and Reech, 1991) and (*b*) perhaps, more significant, by serving to facilitate the response of Aδ and C-polymodal afferents to an otherwise inadequate mechanical or chemical stimulus (Mense, 1981; Heppelmann et al., 1986). The significance of such facilitation has long been suspected in view of the efficacy of cyclooxygenase inhibitors in pain conditions in which an inflammatory state is associated with a clear hyperesthesia, as occurs in arthritis.

The broad relevance of such a facilitatory phenomena is emphasized by physiological studies showing that the large preponderance of C-fibers may only be mildly activated, if at all, even by tissue disruptive stimuli. In contrast, following the development of an inflammatory state, these "silent nociceptors" develop low thresholds and prolonged responses to otherwise innocuous stimuli (Schaible et al, 1987; Schaible and Schmidt, 1988).

Current emphasis has begun to focus on the role of even more potent facilitators other than those whose presence is blocked by cyclooxygenase inhibition. These include leukotrienes and a variety of hydroxylipidic acids (Rackham and Ford-Hutchinson, 1983; Soter et al., 1983; Martin et al., 1987). Of further interest are the hyperalgesic effects of a variety of cytokines (such as interleukins) (Ferreira et al., 1988), many of which possess a complex substrate but can share the property that they can be released from antigen-presenting cells of the immune system when activated. For example, a variety of conditions generated by injury, inflammation, and infection will yield active factors that can serve to stimulate peripheral nerve endings and evoke a pain message or facilitate the response of a high-threshold peripheral nerve ending to a natural and perhaps otherwise nonnoxious physical stimulus.

In the context of the present review, we will now consider in detail the probable contribution of the peripheral adenosine receptor to the generation of the pain message. This focus is warranted by the facts that caffeine, at clinically useful concentrations (section II), has a significant affinity for adenosine receptors (section III) and that it is becoming increasingly appreciated that adenosine plays a complex role in *generating* a portion of the peripheral pain message. This is in contrast to central actions, particularly in the spinal cord, where adenosine may act to suppress nociceptive processing.

B. Peripheral Adenosine Receptors and Nociception

The activation of peripheral adenosine receptors has been shown to evoke and facilitate pain states in humans and animals. Evidence indicating the nature of this pain state and its subsequent underlying mechanisms will be considered.

1. Evocation of a pain and hyperalgesic state by adenosine. a. ALGOGENIC ACTIONS. The activation of sensory nerve terminals by ATP to produce pain has been known or inferred for some time (Keele and Armstrong, 1964; Collier et al., 1966). This action has been demonstrated in the human blister base model, where the direct application of ATP, ADP, and AMP elicits pain (Bleehen et al., 1976; Bleehen and Keele, 1977). The pharmacology of this action has not been studied extensively, but ADP interacts with 5-hydroxytryptamine by exhibiting syn-

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ergy and mutual desensitization (Bleehen and Keele, 1977). Both ATP and ADP produce a direct activation of cation channels in rat sensory neurons (Krishtal et al., 1983, 1988), and this action might account for sensory nerve activation. AMP does not activate cation channels (Krishtal et al., 1983); therefore, its action may be due to conversion to adenosine, because application of adenosine to the blister base preparation also produces pain (Bleehen and Keele, 1977). The mechanism by which adenosine activates sensory nerve endings is considered below.

Other types of studies in humans also indicate that adenosine can elicit pain. Thus, the i.v. administration of adenosine to healthy volunteers and patients with stable angina provokes chest pain (Sylvén et al., 1986, 1987, 1988a). Such pain radiates to the shoulders, arms, epigastric area, back, and throat and does not differ qualitatively from anginal pain (Sylvén et al., 1986). In patients with duodenal ulcer, the pain induced by i.v. administration of adenosine was described as similar to that of ulceration (Watt et al., 1987). The time course of the onset of chest pain by i.v. adenosine was similar to the onset of atrioventricular block (Sylvén et al., 1987), and the pain was proposed to originate from a myocardial site. In a subsequent study, this pain was examined directly by administering adenosine by intracoronary infusion to patients with stable angina (Crea et al., 1990). This precipitated chest pain with a character, location, and radiation similar to anginal pain, and it was concluded that the pain induced by adenosine originated in the heart. Additional sites of action also could be involved, because abdominal pain also was encountered following intraarterial administration. Pain elicited by both i.v. and intraarterial administration of adenosine is blocked by aminophylline (Sylvén et al., 1986; Crea et al., 1990), whereas that produced by i.v. adenosine is potentiated by dipyridamole (which blocks adenosine transport) (Sylvén et al., 1986). The mechanism of the cardiac pain produced by adenosine was proposed as due to activation of cell surface adenosine receptors on sensory nerve terminals in the myocardium.

In view of the induction of cardiac pain by i.v. adenosine and of the observation that intraarterial adenosine induces pain and discomfort in the forearm that is qualitatively similar to that produced by ischemic exercise (Sylvén et al., 1988b), the role of endogenous adenosine in ischemic pain has been examined. Aminophylline reduces exercise-induced chest pain (Crea et al., 1990) and delays the time to onset of angina during exercise-induced ischemia (Crea et al., 1989). Theophylline similarly reduces pain resulting from ischemic work in the forearm (Jonzon et al., 1989). In both cases, however, the pain is not abolished. The reduction of this ischemia-induced pain by methylxanthines suggests that an endogenous release of adenosine with a subsequent activation of adenosine receptors is a significant factor involved in the generation of such pain. However, the partial nature of the block indicates that other factors also are involved.

b. HYPERALGESIA. In animal studies, local application of adenosine to sensory nerve endings by intradermal injection has been shown to produce hyperalgesia using a paw compression test (Taiwo and Levine, 1990). This action is mediated by adenosine A2 receptors because it is elicited by the A2-selective agonists, CV1808 and N-ethylcarboxamide adenosine, but not by the A1 selective-agonist, cyclopentyladenosine; hyperalgesia is antagonized by an A2-selective antagonist but not by an A1-selective antagonist (Taiwo and Levine, 1990). Local administration of adenosine and 2-chloroadenosine to the hindpaw also enhances formalin-induced licking activity, presumably by activation of local adenosine receptors in the paw because licking was inhibited by a local injection of 8-sulfophenyltheophylline, which does not gain access to the CNS (Jonzon et al., 1990). ATP also enhances the nociceptive activity of formalin, but it is not clear whether this is a direct action of ATP or due to metabolism to adenosine.

Although intradermal injection of N-ethylcarboxamide adenosine or *R*-phenylisopropyl adenosine inhibited formalin-induced licking, this action is likely due to a systemic antinociceptive action of these agents, because it was also observed following injection into the contralateral paw (Jonzon et al., 1990). The same explanation may apply to the observation that intradermal cyclopentyladenosine reduced hyperalgesia by CV1808 in the paw compression test (Taiwo and Levine, 1990), although contralateral injections were not performed in this study. A number of studies have demonstrated that systemic administration of adenosine analogs produces antinociception (section VIII.A.1). Although adenosine analogs act at both spinal and supraspinal sites to suppress pain (reviewed by Sawynok and Sweeney, 1989), following systemic administration their primary site of action is believed to be within the spinal cord (Holmgren et al., 1986).

2. Mechanisms of algogenic actions of adenosine. a. DIRECT ACTIVATION OF SENSORY NERVE TERMINALS. A significant component of the pain elicited by adenosine may be due to a direct activation of unmyelinated sensory nerve terminals (fig. 3). Although receptor localization techniques have not demonstrated the presence of adenosine receptors on sensory nerve terminals, adenosine receptors are located on dorsal root ganglion cells because adenosine analogs modify Ca^{2+} currents in these cells (MacDonald et al., 1986; Dolphin et al., 1986). A direct activation of sensory nerve terminals is indicated by the ability of adenosine to increase neuronal activity in renal sympathetic nerves, resulting in hypertension (Katholi et al., 1983), and to increase the rate of discharge of chemoreceptors, resulting in respiratory stimulation (McQueen and Ribeiro, 1986; Monteiro and Ribeiro, 1987). Chemoexcitation induced by adenosine is due to

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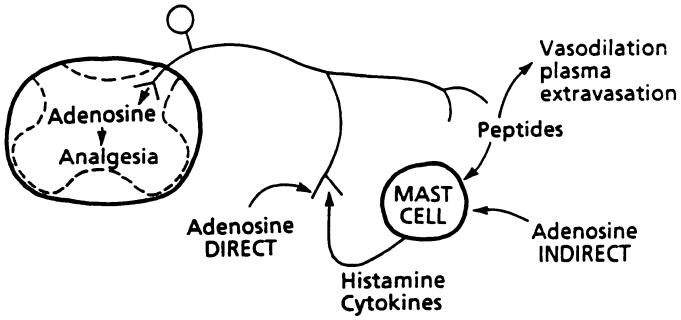

FIG. 3. Potential actions of adenosine on sensory nerves to modulate nociceptive signaling and processing. Adenosine may act at peripheral sensory nerve terminals to activate the nerve terminals directly (section VII.B.2.i), or it may activate such terminals indirectly by modulating the release of mediators from mast cells (section VII.B.2.ii). Within the spinal cord, adenosine acts to suppress nociceptive processing (section VIII.A.1).

activation of adenosine A2 receptors and is reduced by methylxanthines (McQueen and Ribeiro, 1986).

The hyperalgesic action of adenosine also appears to be due to a direct action on sensory nerve terminals. Thus, the time course of the onset of hyperalgesia by adenosine and CV1808 is rapid and consistent with that of other directly acting hyperalgesic agents such as PGE_2 (Taiwo and Levine, 1990). In addition, the hyperalgesia is not altered by chemical sympathectomy, elimination of polymorphonuclear leukocytes, or indomethacin, all of which eliminate hyperalgesia by bradykinin, NA, and leukotriene B_4 (Levine et al., 1984, 1986b) (Taiwo and Levine, 1990). Finally, hyperalgesia produced by CV1808 is prolonged by rolipram, a phosphodiesterase inhibitor. This observation suggests that an increase in cyclic AMP mediates this action of adenosine receptor activation; hyperalgesia produced by the directly acting agents, PGE_2 and prostacyclin (Taiwo et al., 1989) is also prolonged by rolipam.

Local application of caffeine and theophylline has been reported to reduce hyperalgesia produced by intraplantar PGE_2 in indomethacin-pretreated rats using a paw pressure test but enhances hyperalgesia produced by PGE_2 in non-pretreated rats (Ferreira and Nakamura, 1979a). Although the enhancement of hyperalgesia was interpreted as being due to phosphodiesterase inhibition, and considered as evidence for the involvement of cyclic AMP in PGE_2 hyperalgesia, it is very difficult to interpret these observations as they relate to caffeine and theophylline because only one dose was given and methylxanthines are known to have a number of pharmacological properties (section III). No explanation was offered for the reduction in hyperalgesia induced by methylxanthines in indomethacin-pretreated rats, but blockade of a hyperalgesic effect of adenosine released locally might be involved.

b. INDIRECT ACTIONS OF ADENOSINE. An additional mechanism by which adenosine potentially could activate sensory nerve terminals is indirectly via release of mediators, such as histamine, from mast cells (fig. 3), which can stimulate nerve endings to produce itch and pain (Keele and Armstrong, 1964; section VII.A). Mast cells are found in close association or in direct contact with peripheral nerve endings (Newson et al., 1983). Tissue injury and antidromic stimulation of peripheral nerves causes mast cell activation and degranulation (Kiernan, 1971, 1972). This action may be secondary to the release of neuropeptides from sensory nerve terminals, because substance P releases histamine from mast cells (Barnes et al., 1986; Lowman et al., 1988).

Adenosine has been demonstrated to bind to rat serosal mast cell membranes (Marquardt and Wasserman, 1985). Although adenosine itself does not alter mediator release from mast cells, it is capable of modulating release activated by other agents. The direction of the modulation depends on a number of variables including the origin of the mast cells, dose, and time of exposure to adenosine. Adenosine enhances histamine release induced by antigen challenge from rat lung and peritoneal mast cells (Fredholm and Sydbom, 1980; Nishibori et al., 1983; Church and Hughes, 1985) and human lung mast cells (Hughes et al., 1984; Marone et al., 1989) but inhibits such release from human skin mast cells (Marone et al., 1989). Effects of adenosine can be dose dependent, because incubation with submicromolar concentrations of adenosine inhibits evoked histamine release, whereas incubation with higher concentrations enhances such release (peritoneal mast cells, Nishibori et al., 1983). The time of addition of adenosine relative to the addition of secretogogue also can determine the direction of the effect. Thus, pretreatment of human lung mast cells with adenosine prior to an immunological challenge leads to inhibition of histamine release, but addition after the challenge causes enhancement of histamine release (Hughes et al., 1984). Both actions were reduced by methylxanthines and mediated by an adenosine A2 receptor. Release of adenosine from mast cells by immunological challenge has been demonstrated (Marquardt et al., 1984), and it has been proposed that the postrelease facilitation phenomenon has a significant functional role following mast cell activation (Hughes et al., 1984).

Adenosine also modulates histamine release from other cells involved in inflammatory responses. For example, adenosine inhibits histamine release from immunologically stimulated human basophils (Marone et al., 1979, 1985, 1989; Hughes et al., 1987; Peachell et al., 1989). This action is due to activation of an A2 receptor and stimulation of adenylate cyclase (Marone et al., 1985; Hughes et al., 1987), although an additional action may occur following uptake of adenosine into the cell (Hughes et al., 1987; Peachell et al., 1989). As with mast cells, addition of adenosine after the immunological stimulation was reported to potentiate histamine release (Church et al., 1983), but this observation has not been confirmed (Peachell et al., 1989).

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In addition to these effects of adenosine on preformed mediators from inflammatory cells, adenosine can alter the release of newly generated mediators synthesized by the lipoxygenase and cyclooxygenase pathways. There is evidence that basophils and mast cells differ with respect to mediators synthesized (Samuelson et al., 1987; Marone, 1988), and effects of adenosine seem to vary according to cell type. Thus, adenosine and adenosine analogs inhibit immunologically stimulated release of leukotriene C_4 from human basophils (Peachell et al., 1989; Marone et al., 1989) but augment leukotriene C_4 release from human lung mast cells (Marone et al., 1989). Adenosine also inhibits PGD_2 release from human skin mast cells (Marone et al., 1989). Effects of adenosine on the generation of arachidonic acid mediators have not been examined extensively, but in view of the induction of hyperalgesia by a number of such metabolites (leukotriene B_4, prostaglandin E_2, prostacyclin) (Juan and Lembeck, 1974; Levine et al., 1984, 1986a), and of potential modulation in stimulated nociceptive responses by others (leukotriene C_4, leukotriene D_4; Schweizer et al., 1984), such potential actions warrant consideration.

c. SOURCES OF ADENOSINE AT PERIPHERAL NERVE TERMINALS. Within cells, adenosine can arise from the sequential breakdown of ATP by phosphatase and 5′-nucleotidase enzymes, by hydrolysis of S-adenosyl homocysteine by S-adenosyl homocysteine hydrolase, and possibly from cyclic AMP by the action of phosphodiesterase and 5′-nucleotidase enzymes (Stone et al., 1990; Schrader, 1991). Adenosine is subsequently released extracellularly via a bidirectional nucleoside transporter (Fredholm et al., 1983; Jonzon and Fredholm, 1985; White and MacDonald, 1990). Extracellular adenosine also can arise from ATP released from the cell following metabolism to adenosine by ectophosphotase and ecto-5′-nucleotidase enzymes (Pearson, 1985; Gordon, 1986) or from cyclic AMP released from the cell and its conversion to adenosine by ectophosphodiesterase and ecto-5′-nucleotidase (Rosenberg and Dichter, 1989). The respective roles of these pathways for the generation of extracellular adenosine may differ for different cell and tissue types and under different conditions (e.g., physiological versus hypoxic/ischemic conditions or normal versus tissue injury/inflammation conditions).

For adenosine to activate sensory nerve endings to produce pain, adenosine must be released in the vicinity of the nerve ending following appropriate stimulation. Release from activated nerve terminals may occur, because there is evidence for ATP release as a cotransmitter from peripheral nerve endings of somatic and autonomic sympathetic and parasympathetic nerve terminals (reviewed by White, 1988; Westfall et al., 1991). Perhaps of greater relevance is the demonstration of ATP release from peripheral sensory nerve terminals in the perfused rabbit ear following antidromic stimulation of auricular nerves and skin stimulation (Holton, 1959). This release was reduced by denervation but not by sympathectomy (Holton, 1959). It is not clear whether adenosine itself is released from peripheral terminals of sensory nerves, but adenosine (and nucleotides that form adenosine) is released from capsaicin-sensitive afferents in the dorsal spinal cord by elevated K^+ concentrations and capsaicin (Sweeney et al., 1989).

The release of purines from the heart has been studied for some time (Berne, 1963; Gerlach et al., 1963), and adenosine has been proposed as a significant autoregulator of coronary blood flow (Berne, 1964, 1980). Hypoxia, ischemia, and an imbalance between energy supply and demand have been shown to enhance adenosine release from the isolated heart (Berne, 1963; Gerlach et al., 1963; Katori and Berne, 1966; Bardenheuer and Schrader, 1986). The metabolic origin of adenosine released from the heart appears to vary under normoxic and ischemic conditions (Stone et al., 1990; Schrader, 1991). The endogenous adenosine released as part of this autoregulation cycle may be responsible for one aspect of ischemic pain (section VII.B.1). Release of ATP from cardiac monocytes, with the potential to activate sensory nerve endings directly via P2 receptors, also has been directly demonstrated (Forrester and Williams, 1977). In skeletal muscle, a similar function for purines has been proposed. Thus, ATP is released from active skeletal muscle in vitro (Abood et al., 1962; Boyd and Forrester, 1968), and ATP appears in venous effluent from the exercising forearm in vivo (Forrester, 1972). Such released ATP was proposed to play a significant role in the generation of exercise-induced hyperemia and in ischemic muscle pain (Forrester, 1972).

Purine release may occur under conditions of tissue injury or inflammation. ATP is a ubiquitous cell constituent and is released by dead or dying cells. ATP and ADP are released from platelets (Detweiler and Feinman, 1973; Holmsen and Weiss, 1979), and ATP is released by vascular smooth muscle and endothelium (Pearson and Gordon, 1979). These nucleotides may activate sensory nerve endings directly by a P2 receptor or may be converted to adenosine (via phosphatases and nucleotidases) to act via P1 receptors. Release of adenosine from mast cells (Marquardt et al., 1984), neutrophils (Cronstein et al., 1983), and leukocytes (Mann et al., 1986) has been demonstrated. Because adenosine has been demonstrated to have anti-inflammatory effects on neutrophils and other cell types (Roberts et al., 1985; Schrier and Imre, 1986; Schrier et al., 1990; Cronstein et al., 1985; Cronstein, 1991), a role for adenosine as an inflammatory autacoid has been proposed (Cronstein, 1991). Stimulation of sensory nerve endings to produce pain might be one manifestation of such a local release of adenosine.

C. Calcium Flux, Phosphodiesterase, and 5′-Nucleotidase Inhibition

In addition to its actions as an adenosine receptor antagonist, caffeine inhibits phosphodiesterase, mobi-

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lizes intracellular Ca^{2+}, and inhibits 5′-nucleotidase (section III). Some of these actions potentially could play a role in the peripheral activation of sensory nerves. It is unlikely that inhibition of phosphodiesterase, with a subsequent accumulation of cyclic AMP in the peripheral terminal, would produce antinociception, because an increase in nerve terminal cyclic AMP has been implicated in hyperalgesic mechanisms (Taiwo et al., 1989). Likewise, local injection of Ca^{2+} ions into the periphery induces hyperalgesia (Ferreira and Nakamura, 1979a). If this is mediated by an increase in intracellular Ca^{2+} in the peripheral nerve terminal, it is likely that caffeine, by mobilizing Ca^{2+} stores in dorsal root ganglion neurons (Neering and McBurney, 1984), would tend to produce hyperalgesia rather than antinociception. Interestingly, inhibition of 5′-nucleotidase by caffeine (section III.D) at peripheral sites potentially could produce antinociception. Thus, if adenosine is produced endogenously at peripheral nerve endings during inflammatory conditions via release of ATP or cyclic AMP, inhibition of 5′-nucleotidase (which converts 5′-AMP to adenosine) could prevent activation of the nerve ending by adenosine to signal pain.

D. Interactions with Inflammatory Intermediaries

Caffeine has been reported to produce direct anti-inflammatory actions. Such activity was seen in the carrageenan hindlimb edema assay (Vinegar et al., 1976; Seegers et al., 1981) and in the carrageenan pleurisy assay (Vinegar et al., 1976). In addition, caffeine augments the anti-inflammatory actions of cyclooxygenase inhibitors (Vinegar et al., 1976; Seegers et al., 1981). The mechanism of this purported anti-inflammatory effect is not clear. As noted above, the formation of certain local intermediaries, such as the prostaglandins secondary to injury, can facilitate the activation of peripheral afferent terminals (see section IX.A). In one study in which potential effects of caffeine on prostaglandin synthetase activity were addressed, no intrinsic effects of caffeine were noted, and caffeine did not augment the action of aspirin (Vinegar et al., 1976). However, there have been no systematic studies of the effects of caffeine on the various prostaglandin synthetases. Interestingly, caffeine may alter the development of the inflammatory process by altering the disposition of inflammatory cells in response to local inflammation. Thus, caffeine inhibits the migration of neutrophils into a pleurisy exudate in rats (Vinegar et al., 1976). The potential relevance of this early observation was suggested by Zheng et al. (1990) who observed that tumor necrosis factor, a cytokine released from activated mononuclear cells, can cause damage to endothelial cells, an action that is facilitated in the presence of neutrophils. In these in vitro studies, caffeine and other methylxanthines reduced the tumor necrosis factor-induced damage to the endothelial cells when the agents were administered in the presence of neutrophils. Caffeine and other methylxanthines may, therefore, interact subtly with the postinjury processes by altering the cascade of events that lead to the subsequent elaboration of other inflammatory intermediaries.

It should be stressed that a direct or indirect interaction of caffeine with inflammatory processes may account for certain adjuvant actions of caffeine in inflammatory tests. However, such actions cannot reflect the sole effects of caffeine. For example, (*a*) antinociception is frequently seen at considerably lower doses than is the anti-inflammatory effect (4.5 versus 29.2 mg/kg; Seegers et al., 1981), (*b*) caffeine potentiates the antinociceptive effects of aspirin in doses that did not produce intrinsic anti-inflammatory effects (Vinegar et al., 1976), and (*c*) the potentiation observed clinically with caffeine has been observed with agents that vary markedly in their prostaglandin synthesis inhibition activity and yet differ little in their analgesic activity (see section IX.A).

E. Summary

Local tissue injury can physically activate high-threshold afferents and generate a behaviorally defined pain state. Local injury, ischemia, and processes secondary to inflammation and infection, such as the activation of the immune system, will lead to the elaboration of active products that can evoke activity in small afferents by an interaction with the peripheral terminals and, in addition, facilitate the afferent response to a given stimulus (i.e., produce a hyperesthetic state). These intermediaries may include various kinins, elements of the prostaglandin cascade, and purines, notably adenosine. The ability of caffeine to block competitively the actions of adenosine at concentrations readily achieved by commonly used caffeine doses suggests that an interaction with this peripheral action of adenosine may be an important mechanism by which the methylxanthines, in general, and caffeine, in particular, can exert an effect on peripheral pain processing. Additional mechanisms, such as altered migration of inflammatory cells also may by involved.

VIII. Central Mechanisms of Caffeine Interactions with Nociceptive Processing

A. Neuraxial Effects of Caffeine on Nociceptive Transmission

All afferent input is subject to an ongoing process of modulation at each synaptic link. Such modulation, both facilitatory and inhibitory, may result in an ongoing or reflexly evoked change in the magnitude of the excitation evoked by a given afferent stimulus. Such modulation of synaptic excitability is appreciated to occur widely at both spinal and supraspinal sites. Facilitation or inhibition of the modulatory component may lead to a change in the encoded intensity of the afferent-evoked activity within the neuraxis. A review of the pharmacology of caffeine and the methylxanthines (section III) empha-

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sizes that this class of agents, acting at low concentrations, possesses specific interactions with a number of spinal cord, brainstem, and forebrain neurochemical systems, notably those for the adenosine and adrenergic systems. Because these systems have been shown to play a potent interactive role in the central processing of afferent nociceptive transmission at the spinal cord and brain, such changes must be considered as potential mechanisms by which caffeine induces changes in pain behavior in human and animal pain models.

1. Central adenosine receptors and pain transmission. The systemic (Ahlijanian and Takemori, 1985; Holmgren et al., 1986; Herrick-Davis et al., 1989), i.t. (Post, 1984; Holmgren et al., 1986; DeLander and Hopkins, 1986; Sawynok et al., 1986; Sosnowski et al., 1989; Fastbom et al., 1990; Karlsten et al., 1990), and intracisternal or i.c.v. (Yarbrough and McGuffin-Clineschmidt, 1981; Herrick-Davis et al., 1989) administration of adenosine analogs produces antinociception in a variety of tests commonly used to assess activity of centrally active analgesic/antinociceptive agents. The role of adenosine in suppressing central pain transmission has been reviewed recently (Sawynok and Sweeney, 1989). Following systemic administration, the efficacy of adenosine analogs has been attributed to an action on spinal cord processing (Holmgren et al., 1986). The i.t. efficacy of adenosine analogs appears to be due, in part, to antagonism of the actions of mediators of pain signaling within the spinal cord such as substance P and excitatory amino acids (Doi et al., 1987; DeLander and Wahl, 1988).

The presence of both A1 and A2 adenosine receptors in the spinal cord has been demonstrated using binding and autoradiographic techniques (Geiger et al., 1984; Choca et al., 1987, 1988), and both subtypes have been implicated in spinal antinociception. Methylxanthines, including caffeine, reduce the antinociception induced by i.t. administered adenosine analogs. This action, therefore, is unlikely to contribute to antinociception or to the adjuvant actions of caffeine.

Methylxanthines reduce spinal antinociception by morphine (Jurna, 1981, 1984; DeLander and Hopkins, 1986; Sweeney et al., 1987), and this interaction has been interpreted as being due to a morphine-induced release of adenosine from the spinal cord. Such release has been demonstrated directly both in vitro and in vivo (Sweeney et al., 1987, 1989). Methylxanthines also reduce antinociception following supraspinal administration of morphine (DeLander and Hopkins, 1986; Sweeney et al., 1991), and again, this appears to be due to an antagonism of adenosine released from the spinal cord by i.c.v. morphine; this effect has been demonstrated directly (Sweeney et al., 1991).

Other central actions of morphine also are blocked by methylxanthines, although implications for pain transmission are not readily apparent. In the cortex, caffeine reduced the inhibition of acetylcholine release produced by morphine (Jhamandas et al., 1978; Phillis et al., 1980), and in the striatum, methylxanthines antagonize the inhibition of neuronal firing caused by morphine (Perkins and Stone, 1980). The interaction in the cortex may be due to adenosine release by morphine, because morphine enhances the release of radiolabeled adenosine from the cortical surface in vivo (Phillis et al., 1979; Jiang et al., 1980; but see Jhamandas and Dumbrille, 1980) and enhances stimulus-evoked release from cortical slices in vitro (Fredholm and Vernet, 1978; Stone, 1981; Wu et al., 1982).

Although it appears that the spinal antinociceptive action of adenosine and its antagonism by methylxanthines runs counter to any negative modulation of nociceptive processing within the spinal cord, it should be noted that spinal effects of adenosine on nociceptive processing at the cellular level are not completely characterized. Although models of acute pain (tail flick, hot plate) have been used in most behavioral studies, there is a growing appreciation that the clinical state may be more clearly reflected by models in which protracted afferent stimulation is used. It has been shown that repetitive C-fiber barrages lead to a state of facilitated spinal processing, referred to as windup (Mendell, 1966), a process mediated at the spinal level by NMDA receptor activation; the spinal application of NMDA antagonists can inhibit windup (Dickenson and Sullivan, 1990). NMDA antagonists function poorly in tests with acute nociceptive stimuli but are extremely effective in animal models in which protracted stimuli may evoke a central facilitation (Yaksh, 1989; Yaksh and Yamamoto, 1991). Ketamine, an NMDA receptor antagonist, is clinically known to be a good analgesic in certain pain states (Slogoff et al., 1974; White et al., 1982), suggesting the probable relevance of NMDA-mediated facilitated pain states in human clinical pain. Recently, it was demonstrated that adenosine can enhance the depolarizing response of NMDA in cortical slices, and this effect is blocked by theophylline (Mally et al., 1990). It is conceivable that adenosine may have unique actions on a protracted pain stimulus and that inhibition of this action might alter nociceptive processing by diminishing the magnitude of the facilitated state.

2. Central noradrenergic systems. Noradrenergic systems in brain and spinal cord play complex and often apparently opposing roles in the modulation of nociceptive transmission. As reviewed elsewhere (Yaksh et al., 1988), it is currently appreciated that the analgesic effects of supraspinally administered opiates are mediated, in part, by the activation of bulbospinal noradrenergic and serotonergic pathways. These pathways originate from catecholamine- and indoleamine-containing cell bodies in the pons (such as the locus coeruleus, lateral tegmentum) and in the medial medulla (caudal raphe). In the spinal cord, increased activity at noradrenergic terminals, as mimicked by the i.t. injection of NA, will

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increase the nociceptive threshold (i.e., produce analgesia) (for review, see Yaksh, 1985) and produce a synergistic interaction with spinal opioids (Monasky et al., 1990; Ossipov et al., 1990, and references therein).

At the spinal level, i.t. methylxanthines do not influence the receptor-mediated analgesic actions of NA (Sweeney et al., 1987; DeLander and Hopkins, 1987). However, interactions with supraspinal NA mechanisms may contribute to adjuvant and analgesic actions of caffeine. Caffeine enhances NA turnover in several brain regions (Berkowitz et al., 1970; Waldeck, 1971; Corrodi et al., 1972; Goldberg et al., 1982; Hadfield and Milio, 1989). This action may result from disinhibition of NA neurons in the locus coeruleus, because adenosine has been shown to inhibit the firing of neurons in the locus coeruleus in an in vitro preparation by a methylxanthine-sensitive mechanism (Shefner and Chiu, 1986; Regenold and Illes, 1990). This action appears to be due to an enhancement of K^+ conductance and is mediated by an adenosine A1 receptor (Regenold and Illes, 1990). Adenosine also inhibits NA release from central NA nerve terminals (Harms et al., 1978; Jonzon and Fredholm, 1984; Jackish et al., 1985).

Within the locus coeruleus, adenosine appears to be tonically active, as an inhibitor of adenosine uptake also inhibits neuronal firing by an action that is blocked by an adenosine A1 receptor antagonist (Regenold and Illes, 1990). Although 3-isobutyl-1-methylxanthine enhances firing of neurons in this region (Grant and Redmond, 1982), and this could be interpreted as further evidence for tonic activity of adenosine in the locus coeruleus, 3-isobutyl-1-methylxanthine is a potent phosphodiesterase inhibitor, and the increase in firing could be due to an increase in cyclic AMP levels in locus coeruleus neurons (Wang and Aghajanian, 1987). Because bulbospinal NA pathways have been directly implicated in the action of morphine (Yaksh et al., 1988), an enhancement of NA turnover in bulbospinal pathways by caffeine might well contribute to an enhancement of opioid antinociception. Such a mechanism has been implicated in the enhancement of antinociception by baclofen (Steardo and Sawynok, 1985), but this possibility has not been directly assessed for morphine.

Bulbospinal NA pathways appear to be tonically active, exerting an ongoing reflex inhibition of nociceptive thresholds (Sagen and Proudfit, 1984). Additionally, noxious stimulation results in spinal release of NA which is mediated by an activation of a supraspinal loop (Tyce and Yaksh, 1981). Methylxanthine-induced antagonism of the action of adenosine in the locus coeruleus (which would dampen this mechanism) could augment this aminergic feedback mechanism and produce analgesia.

In addition to the bulbospinal pathways emphasized above, NA pathways projecting to the forebrain are implicated in antinociception by studies in which morphine was used (reviewed by Sawynok, 1989a). The most relevant observations are that (*a*) analgesic doses of morphine increase levels of 3-methoxy-4-hydroxy ethylene glycol SO_4, a major metabolite of NA, in certain forebrain regions (Roffman et al., 1977, 1979; LoPachin and Reigle, 1978) and (*b*) 6-hydroxydopamine-induced lesions to the dorsal bundle, which selectively deplete NA in the forebrain, potentiates antinociception by morphine (Price and Fibiger, 1975; Sawynok, 1989a). Interestingly, the potential role of forebrain NA projections in psychomotor stimulant properties of caffeine (section VI.B) may provide one interface between psychomotor effects of caffeine and antinociception.

3. Benzodiazepine/γ-aminobutyric acid interactions. a. BENZODIAZEPINES. Benzodiazepines, although antianxiolytic, are not generally considered to have analgesic properties, but spinal administration of benzodiazepines have been reported to have antinociceptive actions (Yanez et al., 1990). There are a number of reports that systemic administration of benzodiazepines antagonizes antinociception by opioids (Mantegazza et al., 1982; Abbott and Franklin, 1986; Palaoglu and Ahyan, 1986; Rosland et al., 1990). Some investigators have reported that caffeine binds at the benzodiazepine site and antagonizes certain actions of benzodiazepines (section III.F). If this antagonism occurred at pharmacologically relevant concentrations of caffeine, this action might enhance antinociception. Consistent with this possibility, caffeine has been shown to reverse the diazepam-induced inhibition of antinociception by morphine (Zambotti et al., 1986).

b. γ-AMINOBUTYRIC ACID A INTERACTIONS. The systemic administration of $GABA_A$ agonists (muscimol, THIP) produces antinociception in a variety of tests (Hill et al., 1981; reviewed by Sawynok, 1989b). Although both spinal (Hammond and Drower, 1984) and supraspinal (Liebman and Pastor, 1980; Baumeister and Frye, 1986) sites have been implicated in such actions, it is difficult to separate the spinal antinociceptive action from motor incoordination (Hammond and Drower, 1984). Caffeine has been noted to inhibit $GABA_A$ receptor-Cl^- channel coupling (section III.F), but it is not clear how such an action might serve to augment antinociception in view of the suppression of nociception by $GABA_A$ agonists. Effects of methylxanthines on muscimol- or THIP-induced antinociception have not been reported.

c. γ-AMINOBUTYRIC ACID B INTERACTIONS. The systemic administration of the $GABA_B$ agonist baclofen also produces antinociceptive activity in a variety of tests (Hill et al., 1981; reviewed by Sawynok, 1989b). Both spinal (Wilson and Yaksh, 1978; Hammond and Drower, 1984) and supraspinal (Levy and Proudfit, 1979; Liebman and Pastor, 1980) sites are implicated in the actions of baclofen, although following systemic administration the action appears to occur predominantly at supraspinal sites (Proudfit and Levy, 1978). Both caffeine and the-

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ophylline, given systemically, augment antinociception produced by systemically administered baclofen (Sawynok, 1983), probably as a result of an enhancement of NA activity in bulbospinal pathways, because these effects are directly implicated in the action of baclofen (Sawynok and Dickson, 1985). In addition, clonidine reverses both the activation of NA neurons in the locus coeruleus by methylxanthines (Grant and Redmond, 1982) and the methylxanthine-induced potentiation of the action of baclofen (Steardo and Sawynok, 1985).

4. Calcium fluxes and phosphodiesterase inhibition. Morphine affects central Ca^{2+} disposition in a number of ways, including decreasing Ca^{2+} levels and decreasing Ca^{2+} uptake into nerve terminals (reviewed by Chapman and Way, 1980). The supraspinal administration of Ca^{2+} antagonizes antinociception by morphine (Hano et al., 1964; Harris et al., 1975; Chapman and Way, 1982), whereas spinal Ca^{2+} administration augments antinociception by morphine (Lux et al., 1988; Sawynok et al., 1990). Supraspinally, it is not clear whether the effect of Ca^{2+} on morphine is due to an increased intracellular concentration of Ca^{2+} resulting from increased penetration of the exogenous Ca^{2+} into the cell or to cell-surface interactions due to the release of intermediary factors. If morphine antagonism is due to an increase in intracellular Ca^{2+}, then intracellular release of Ca^{2+} by methylxanthines would mimic exogenous Ca^{2+} administration and antagonize antinociception. By the same reasoning, within the spinal cord, methylxanthines might enhance opioid antinociception. However, this is not observed experimentally for i.t. methylxanthines (section V.D), and the intrinsic antinociceptive effects of Ca^{2+} following i.t. administration appear to be secondary to a release of adenosine and, perhaps, NA (Sawynok et al., 1990) and, therefore, may not be directly mediated by an increased intracellular availability of Ca^{2+}.

Morphine and other opioids are negatively coupled to the adenylate cyclase system (Sharma et al., 1975; Law et al., 1981; Cooper et al., 1982), although some evidence exists for a positive modulation at some sites (Makman et al., 1988). The role of cyclic AMP in mediating antinociception produced by morphine, both at supraspinal sites (Hosford and Haigler, 1981) and in the spinal cord (Nicholson et al., 1991b), has received some attention, but complex effects have been observed with agents that interact with the cyclic AMP system (e.g., forskolin, phosphodiesterase inhibitors); both inhibition and augmentation of the actions of morphine have been observed (Nicholson et al., 1991b).

It is unlikely that the central effects of caffeine observed following systemic drug administration are due to a central inhibition of phosphodiesterase because of the dose requirement for such an action (section III). It is not clear to what extent this action accounts for the effects of methylxanthines on nociceptive thresholds when methylxanthines are given by injection into the spinal cord where local concentrations may be much higher. Accordingly, whereas lower doses of i.t. methylxanthines reduce spinal and supraspinal effects of morphine (DeLander and Hopkins, 1986; Sweeney et al., 1991; Nicholson et al., 1991b) due to an adenosine receptor antagonism, higher doses of methylxanthines (as well as nonxanthine phosphodiesterase inhibitors) augment spinal (Nicholson et al., 1991b) and supraspinal (Sweeney et al., 1991) antinociception by morphine.

B. Methylxanthine Dependence and Withdrawal

Chronic administration of caffeine and other methylxanthines leads to tolerance to the psychomotor and physiological actions of that agent. Removal of the agent for a period, which permits its clearance (3 to 24 h), results in a reduced locomotor function (Boyd et al., 1965; Holtzman, 1983; Finn and Holtzman, 1986), disruption of operant behavior (Carney, 1982) in animals and humans, irritability, muscle twitching, and headaches (Greden et al., 1980; Stringer and Watson, 1987; Smith, 1987; Griffiths et al., 1986, for review, see Griffiths and Woodson, 1988c). Subjects undergoing voluntary cessation of caffeine intake displayed a transient, but significant, incidence of headache frequency during the next 2 to 3 days (Van Dusseldorp and Katan, 1990). These observations have led to the speculation that under a number of conditions, such as following surgical procedures when normal food consumption is restricted (Fennelly et al., 1991) or in the case of agent abuse when the subject may abuse large quantities of caffeine (Baumgartner et al., 1989), there may be a hypersensitive state that would be treatable with a caffeine-containing medication.

The mechanisms of this withdrawal discomfort are not understood. Although chronic caffeine intake results in a modest upregulation of adenosine receptors (section VI.B), this does not appear to account for tolerance to caffeine (Finn and Holtzman, 1987; Holtzman et al., 1991). Caffeine withdrawal has been shown to increase intracranial blood volume (Mathew and Wilson, 1985), a phenomena apparently reversed by caffeine treatment. Such a mechanism has been speculatively offered for the ability of caffeine to diminish headaches accompanied by low CSF pressures (section IV.B).

It appears likely that several mechanisms may well be involved in the discomfort associated with caffeine withdrawal. Thus, Griffiths and Woodson (1988c), in their review of the human literature, emphasized that (*a*) caffeine withdrawal-associated fatigue and mental state could occur in the absence of reported headaches and (*b*) fatigue could precede the report of a headache. It should be emphasized that relatively few studies of the biochemistry of the caffeine withdrawal state have been accomplished. Thus, in one of the few studies, Kirch et al. (1990) noted that, following administration of caffeine to mice for 30 days, the content of brain dopamine, NA,

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and 5-hydroxytryptamine was increased, suggesting a decreased release. Speculatively, in the withdrawal phase, this would be associated with augmented CSF secretion.

C. Alterations in the Affective Component of Pain

The response evoked by a given high-intensity stimulus event is markedly dependent on the psychological state of the organism. This reflects on the notion that the pain state in humans and animals possesses not only an intensity-discriminative component but also an affective-motivational component (Melzack and Casey, 1968; Melzack and Wall, 1973). In addition to the effects that caffeine-sensitive systems might play in the transduction of the physical stimulus and the processing of the afferent message, caffeine has potent CNS effects on the psychological state of humans and animals which potentially may modify the affective component of pain. Because of the difficulty in assessing the affective component in an animal model, the role of central drug-induced changes in affective state on pain processing/behavior remains controversial. It is significant that overlap between pathways traditionally considered to be related to changes in affective behavior are being shown to exert correlated effects on the organized response of the animal to an ongoing painful stimulus (Franklin, 1989). Clearly, these perceptual components can alter the response of humans to a given noxious stimulus. Thus, enhanced depressive states (Turner and Romano, 1984; Romano and Turner, 1985; Kremer et al., 1983) and increased anxiety (Beecher, 1969; Katon, 1984) will lead to lower indices of satisfaction and higher indices of the pain state (Chapman, 1985; Taenzer et al., 1986). These elements, although more poorly understood, have been shown to impact clearly on the response made by the patient/subject to a given physical state that typically evokes a pain complaint. Thus, positive mood states or favorable anticipation of an event may diminish the reported severity of the pain condition, whereas negative mood factors, such as depression or aversion, may augment the reported severity of the state (Johnson, 1973; Chapman, 1985). Indeed, the perceptual and anxiolytic effects of systemically administered strong analgesics are widely appreciated and considered to be an important component of their action (Lasagna et al., 1955; Kaiko et al., 1981). Moreover, the potential significance of even modest alterations in mood on pain states is readily borne out by the utility of antidepressants (such as tricyclic antidepressants), psychomotor stimulants (such as amphetamine), or mood-altering agents (such as amphetamines and cannabanoids) as adjuvant agents in managing various pain states in association with typical analgesics (Bonica et al., 1990; Kaiko et al., 1987; Forrest et al., 1977; Ward et al., 1984, 1985). Although some of these agents may exert their effect directly on the processing of sensory information (for example, by interactions with bulbospinal noradrenergic pathways, see section IX.B.3), in many cases, these agents are said to exert their effect at doses which alone do not produce a significant relief of reported pain. Thus, although the precise role of such drug-induced alterations in mood and aspects of changes in perceptual bias remain to be adequately described, the current evidence clearly supports a contributory role of such changes in ameliorating the reported impact of the pain state.

Caffeine administration in humans resembles the effects seen after administration of other psychomotor stimulants, including amphetamine and fenfluramine (Chait and Johanson, 1988; Chait et al., 1985, 1986a,b, 1987). Despite this similarity, as noted in section VI.B, there is ample evidence to conclude that there are clear distinctions between the functional and pharmacological properties of the methylxanthine and nonmethylxanthine stimulants in animal studies.

In humans, low doses of caffeine (10 to 200 mg) induce mildly positive mood states and stimulant-like effects. At higher doses (>300 mg), a subjective dysphoria has been noted (Chait and Johanson, 1988; Griffiths et al., 1986; Griffiths and Woodson, 1988a,b; Stern et al., 1989). These properties resemble the biphasic effects observed on psychomotor performance in animals following systemically administered methylxanthines, whereby low doses produce stimulation but higher doses produce depression (section VI.B). Given the positive impact of caffeine on mood, it is a reasonable speculation that caffeine may contribute to analgesia (as opposed to antinociception) by virtue of these positive changes in the affective state. The importance of such psychological variables to the behavioral syndrome observed in the presence of an ongoing pain state (as opposed to a reflex function) remains, however, to be systematically examined in a well-defined animal model.

D. Summary

Systems by which caffeine may interact with nociceptive processing may be considered on the basis of those that modify afferent processing and those that result in changes in the affective state of the animal. Based on the pharmacology of the action of caffeine, several mechanisms of interaction may occur. (*a*) Spinal administration of adenosine analogs produces an antinociception that is blocked by methylxanthines, including caffeine, suggesting that an action of caffeine at this site does not contribute to analgesia. However, the role of adenosine in spinal integration of inflammatory pain or in situations involving windup or activation of silent C-fibers has not been examined. (*b*) CNS aminergic systems have been shown to modulate the processing of high-threshold afferent input. Caffeine augments aminergic turnover and may well modulate afferent transmission by this mechanism. (*c*) Interactions with benzodiazepines have been shown to occur, but the significance of this inter-

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action is not known. (*d*) Phosphodiesterase inhibition and Ca^{2+} mobilization appear to interact in a complex manner with opioids. The potential for caffeine interactions with such systems to facilitate the action of opioids is discussed. (*e*) Methylxanthine withdrawal represents an iatrogenic state that is common and amenable to relief with caffeine. The mechanism of the induced headaches is not known but may be vascular in origin. (*f*) In addition to effects on sensory processing, caffeine has psychomotor stimulant properties and, at therapeutically used concentrations, can induce positive changes in mood. Although the mechanisms underlying these changes are not known, the interaction of caffeine with brainstem monoaminergic systems, as well as the known effects on adenosine receptors, is consistent with animal models in which changes in monoamine turnover have classically been associated with changes in affective state.

IX. Interactions between Caffeine and Analgesic Systems

In the preceding two sections, the potential role of caffeine interacting with several pharmacologically defined systems in the periphery and within the neuraxis have been reviewed with respect to providing an assessment of the possible mechanisms by which it may alter nociceptive processing. Caffeine has, however, been largely examined in the context of the actions of two other classes of agents, notably the NSAIDs and the opioids. In the following section, the mechanisms whereby the actions of these other analgesic systems may be specifically altered will be considered.

A. Caffeine-Nonsteroidal Anti-Inflammatory Drug Interactions

NSAIDs can produce a significant analgesia in humans. The inhibition of cyclooxygenase is commonly cited as the mechanism whereby NSAIDs exert their salutary effects on pain states generated after tissue injury (Ferreira, 1972; Ferreira et al., 1973). As discussed in section IV, results of clinical studies have indicated that caffeine may have significant facilitatory effects on the analgesia produced by several NSAIDs, including aspirin, acetaminophen, and ibuprofen. The mechanisms by which this interaction may occur is of particular interest. Several alternatives are possible.

1. Pharmacokinetics. A decreased gastric pH might increase drug clearance from the stomach into the vasculature. At normal oral doses, caffeine has been shown to have only modest effects on NSAID kinetics. In humans, but not rodents, caffeine produces modest increases in peak salicylate and ibuprofen plasma concentrations, whereas both increases and decreases in acetaminophen kinetics have been reported (see section II.F). Such observations do not support changes in NSAID disposition as an explanation for the facilitatory effects of caffeine.

2. Peripheral action. As reviewed in section VII.A, prostanoids can facilitate afferent transduction and augment (or mediate) the inflammatory state, and inhibition of prostaglandin synthesis can diminish that hyperalgesic state and reduce the magnitude of inflammation. As noted above, however, the analgesic potency of this structurally diverse class of agents (NSAIDs) does not covary uniquely with the potency of these agents as cyclooxygenase inhibitors in animal or human models of pain (Brune et al., 1991; Clissold, 1986; Flower et al., 1985). The best example of such a dissociation is acetaminophen which, in contrast to aspirin, is a weak inhibitor of cyclooxygenase and possesses poor anti-inflammatory properties (Rainsford, 1985); yet the clinical analgesic potencies of the two drugs do not differ essentially.

There is a growing appreciation that a number of the NSAIDs may exert potent peripheral effects via non-prostaglandin-mediated mechanisms. Thus, Weissmann (1991) speculated that a variety of NSAIDs may interact directly with G-protein-dependent events leading to neutrophil activation. Such interactions have been shown to diminish the ability of neutrophils to become adherent to the vascular endothelium and diminish their movement though the vascular wall to a site of injury (Abramson et al., 1985, 1991). Importantly, as noted in section VII.D, caffeine also appears to alter the disposition of inflammatory cells in response to local injury, and this could serve to modify the magnitude of the response induced by injury. Studies of the joint interaction of caffeine with "indirect" mechanisms of the peripheral actions of NSAIDs on the inflammatory response would appear to be warranted.

At peripheral sites, there is increasing evidence that adenosine can activate sensory nerve endings to produce pain and hyperalgesia (section VII.B). Potential interactions between adenosine and other agents that can stimulate sensory nerve endings have not been examined, but in view of the variety of agents that can produce such an action, it is conceivable that synergistic interactions may occur. During the last decade, much of the pharmacology of caffeine in humans has been appreciated in terms of antagonism at adenosine receptors because this action occurs at doses encountered after human ingestion of caffeine (generally 10 to 100 μM). Antagonism of a pain facilitatory role of adenosine at the peripheral nerve terminal (and of potential interactions between adenosine and other agents) would clearly serve to augment analgesia by peripherally acting analgesic agents, regardless of whether they act by decreasing prostanoid synthesis or by influencing the migration of inflammatory cells; these actions would result in a reduction in release of inflammatory mediators at the peripheral nerve terminal.

3. Central action. Although there appears little doubt that peripheral events can evoke a hyperesthesia that is

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mediated by the release of certain prostaglandins, this peripheral action alone does not represent a sufficient explanation for the antinociceptive effects of cyclooxygenase inhibitors. Thus, (*a*) intracerebral or i.t. injection of NSAIDs, at doses that are inactive after systemic administration, will produce a powerful attenuation of the behavioral response to certain types of noxious stimuli, indicating a central action of the agent (Yaksh, 1982; Ferreira et al., 1978; Malmberg and Yaksh, 1992); and (*b*) similarly, thalamic neuronal activity evoked by the electrical activation of peripheral nerves can be attenuated by NSAIDs (Carlsson and Jurna, 1987; Groppetti et al., 1988; Jurna and Brune, 1990). In humans, NSAIDs have been shown to alter the magnitude of late-phase tooth pulp stimulation-evoked potentials, although there were no changes in their latency (Chen and Chapman, 1980). These observations suggest that the NSAIDs can exert a central action.

Studies of central release have emphasized that prostaglandins are released into the extravascular extracellular space from spinal (Yaksh, 1982) and supraspinal (Romero et al., 1984; Navarro et al., 1988, 1989) sites secondary to neuronal activity. Classically, prostaglandins (such as PGE_1) have been shown to exert an inhibitory effect on noradrenergic terminals (Stjärne, 1972), and cyclooxygenase inhibitors will increase the turnover of catecholamines and 5-hydroxytryptamine (Groppetti et al., 1988; Paalzow, 1973). It appears likely that, given the ability of afferent stimulation to yield central release of lipidic acids and the ability of such products to facilitate certain aspects of afferent nociceptive processing, cyclooxygenase inhibitors may well exert a central action.

At the spinal cord level, bulbospinal pathways are known to modulate high-threshold afferent input (Yaksh and Aimone, 1988). An alternative mechanism of NSAID actions may thus include a facilitation by NSAIDs of the increased turnover of these bulbospinal aminergic pathways. Such mechanisms have been cited to account for the analgesic effects of NSAIDs in the spinal cord, where bulbospinal noradrenergic pathways have been shown to attenuate dorsal horn activity evoked by primary afferent input (Levine and Taiwo, 1986). As noted above, caffeine and methylxanthines share the possibilities of increasing the outflow from the brainstem by removing a possible tonic inhibition on the cell bodies exerted by adenosine. The nature of the interaction of caffeine with prostaglandins at the levels of the bulbospinal terminal has not as yet been systematically studied, but the above data suggest the possibility of a synergic interaction.

Given the several potential mechanisms whereby NSAIDs may exert their action, there is a growing appreciation that there is a significant dissociation between the analgesic actions of NSAIDs and their activity as inhibitors of prostaglandin synthesis. The best example of this discrepancy is that of aspirin and acetaminophen, both of which are reported to be equally active as analgesics (see section IV; table 1; Cooper, 1981); yet only the former has significant cyclooxygenase inhibitory properties. Given this fundamental difference between these two agents, it appears unlikely that both exert their actions by the same mechanism. Yet, both agents appear to be equally facilitated by caffeine. Whether this indicates that caffeine acts via different mechanisms with the two NSAIDs is unknown.

4. Headache. Headache is a widely used general descriptor that encompasses a large number of clinically defined disorders. In addition to intensity, the varying characteristics of headaches make it clear that the mechanisms of these various pain states will also vary and be differentially sensitive to drugs having different mechanisms of action. Thus, syndromes classified as muscle tension headaches are particularly sensitive to aspirin, whereas migraines are not. Among cluster headaches, syndromes classified as chronic paroxysmal hemicrania are particularly sensitive to NSAIDs, whereas episodic or chronic cluster headaches are not (Kudrow, 1991).

Considerable work has been directed at the mechanism and origin of migranous headaches. Moskowitz and colleagues (1988, 1989) have shown that the antidromic release of substance P from the afferent plexi surrounding cerebral vessels may stimulate inflammatory cells, leading to direct activation of small afferents. The observation that caffeine may alter the migratory characteristics of neutrophils (section VII.D) and modulate release of mediators from mast cells (section VII.B.2b) raises the possibility that some actions of methylxanthines may occur not only because of an effect on the smooth muscle or by the blockade of the dilatory effects of adenosine (Winn et al., 1981) but also by indirect mechanisms.

As noted, caffeine abstinence in a person consuming significant quantities of caffeine daily can induce a headache state, and that sudden abstinence is accompanied by significant increases in blood flow in the frontal poles. The headache and changes in flow can be abolished by the subsequent administration of caffeine (see section IV.B.2a). Given the widespread consumption of caffeinated beverages, it is generally appreciated that a significant fraction of the incidence of headaches experienced in the population may be iatrogenic (Smith, 1987; Fennelly et al., 1991). Caffeine alone, in routinely administered doses (100 to 200 mg, p.o.), is able to reverse these abstinence signs (Goldstein, 1964; Shorofsky and Lamm, 1977).

Significantly, we are not aware of any study in which the interaction of NSAIDs with caffeine has been addressed in such a state. Anecdotal information has, in fact, argued against the activity of analgesics alone in this headache state (Greden et al., 1980). In addition to direct interactive effects, the ability of caffeine to facilitate the effects of NSAIDs on headache may reflect the

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multiple etiology of headache complaints in a clinical population. The development of clinical studies focusing on the caffeine withdrawal headache and the interaction between NSAIDs and caffeine should be addressed.

B. Caffeine-Opioid Interactions

1. Pharmacokinetics. Altered pharmacokinetics of morphine have been implicated in the ability of caffeine to augment antinociception by morphine (Misra et al., 1985), but consistent effects of caffeine on morphine disposition have not been observed (section II.F).

2. Peripheral action. Antinociception produced by opioids is generally attributed to the activation of opioid receptors in the CNS. However, under conditions of peripheral inflammation, opioids appear to produce antinociception by interacting with local opioid receptors in peripheral tissues (Ferreira and Nakamura, 1979b; Joris et al., 1987; Stein et al., 1988, 1989). Activation of peripheral opioid receptors by β-endorphin released by inflammatory cells during stress has been implicated in antinociception (Stein et al., 1990a,b). Caffeine has been shown to stimulate β-endorphin release into the circulation but not into the CSF (Arnold et al., 1982). Although i.v. β-endorphin can produce antinociception (Tseng et al., 1976), the doses required are high compared to physiological concentrations of β-endorphin, and it is questionable whether circulating β-endorphin gains access to the CNS to produce antinociception. However, it is conceivable that physiological amounts of β-endorphin exert a peripheral antinociceptive action under inflammatory conditions (Stein et al., 1990a,b). There is also some evidence that β-endorphin may produce peripheral antinociception under noninflammatory conditions, because i.v. corticotropin releasing factor, which elevates plasma β-endorphin levels, produces antinociception in the hot plate test; this antinociception is reduced by naltrexone methylbromide, a compound that does not gain access to the CNS (Hargreaves et al., 1990).

3. Central action. Opioids act within the CNS both at spinal and at supraspinal sites to suppress manifestations of noxious peripheral stimulation (Yaksh and Noueihed, 1985; Yaksh et al., 1988). Within the spinal cord, opioids decrease the release of neurotransmitters present in small-diameter primary afferent nerve terminals (Jessell and Iversen, 1977; Yaksh et al., 1980; Pohl et al., 1989) and exert a direct inhibitory action on elements postsynaptic to afferent terminals (Zieglganzberger and Bayeryl, 1976; Dickenson et al., 1987; Fleetwood-Walker et al., 1988; Hope et al., 1990). Interestingly, morphine releases adenosine from the spinal cord, and this may contribute directly to spinal antinociception by morphine (Sawynok et al., 1989). When administered locally in the spinal cord, caffeine inhibits antinociception by morphine, an action attributed to antagonism of adenosine released by morphine (section VIII.A.1). This component of action cannot account for augmentation of the actions of morphine as has been reported in a number of studies (section V.D).

At supraspinal sites, opioids are known to act within the mesencephalic periaqueductal gray and the medial and paramedial medulla to alter nociceptive processing by activation of a series of distinct neurotransmitter systems, particularly bulbospinal NA and 5-hydroxytryptamine pathways (Yaksh et al., 1988). A significant portion of the antinociceptive effect of supraspinally administered opioids is, in fact, mediated by the indirect activation of such pathways (Yaksh, 1985). More recently, there has been a growing appreciation that effects of opioids on affective components of behavior may be mediated in part by rostrally projecting aminergic systems. Such pathways may also play a direct role in antinociception as well. Inactivation of serotonin and noradrenergic terminals with neurotoxins and depleting agents leads to an increased irritability of the animal (Yaksh and Aimone, 1988). The observations that caffeine can facilitate the turnover of monoamines (section VIII.A.2) provides a mechanism whereby methylxanthines could significantly facilitate the antinociceptive actions of opioids, not only by enhancing the activation of the bulbospinal pathways and thereby diminishing the afferent traffic but also by augmenting the effects of opiates on affective tone. Systematic studies are required to investigate these several alternatives.

X. Concluding Comments

Pain behavior in humans and animals reflects on the state initiated by certain unconditioned stimuli that generate activity in small primary afferents or in central systems themselves otherwise activated by small afferents. The state is manifested by the verbal report or emitted responses reflecting the aversive nature of the state generated. This input enters the spinal and medullary dorsal horn and initiates patterns of activity in ascending links that reach supraspinal systems. Given the general complexity of the systems that encode sensory information, it is not surprising that, in addition to the anatomical links and the activity generated in certain populations of these supraspinal neurons, little is known regarding the details of the supraspinal elements of the processing evoked by activity in C-fibers. Our growth in understanding of how these signals are generated and eventually processed constitutes a major growth area in neurosciences today. As our understanding of the system is enhanced, rational explanations of how a drug, such as caffeine, may intervene in that signal processing may be developed.

In addition, although it has been appreciated for the last 20 years that changes in the affective state of the organism can alter the response to pain, it has been difficult to translate that appreciation into specific insights. The ability of caffeine and its congeners to produce subtle, but highly discriminable, changes in affect

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and mood represents an important insight into the manner by which drug-induced changes in the affective state can effectively ameliorate a debilitating psychological component of the pain state. Whether this influence on mood reflects on the "stimulant" properties of caffeine or a distinct effect remains to be seen. Interestingly, the subtlety of its action, which gives rise to controversy as to the efficacy of caffeine, probably accounts for the use to be widespread. Arguably, were caffeine to be more effective at altering mood state, its wide spread use might well not be acceptable.

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