Pharmacology Biochemistry & Behavior, Vol. 29, p. 409. Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

INTRODUCTION

Progress in Understanding the Relationship Between the Adenosine Receptor System and Actions of Methylxanthines

JONATHAN L. KATZ* AND JOHN M. CARNEY†

**Preclinical Pharmacology Branch, NIDA Addiction Research Center*
P.O. Box 5180, Baltimore, MD 21224
and †Department of Pharmacology, University of Oklahoma Medical School
Oklahoma City, OK 73190

RESULTS suggesting that the behavioral effects of methylxanthines may be related to their antagonist actions at adenosine receptors has renewed interest in the behavioral effects of methylxanthines. The most widely used and studied methylxanthine is caffeine, which is of course consumed in large quantities in caffeine-containing beverages. However, caffeine is consumed in other forms, and other methylxanthines, specifically theobromine and theophylline, exist in beverages and foods, as well as medicines.

The following group of papers come from a symposium entitled: *Progress in Understanding the Relationship Between the Adenosine Receptor System and Actions of Methylxanthines* held during the Fall 1986 meeting of the American Society for Pharmacology and Experimental Therapeutics in Baltimore, MD. The papers represent different aspects of the pharmacology of methylxanthines.

Holtzman and Finn examine the stimulation of locomotor activity produced by caffeine and the tolerance induced to this effect by chronic caffeine consumption. These authors demonstrate some intriguing differences in tolerance to different behavioral effects of caffeine suggesting at least two types of tolerance to the effects of caffeine. Important for the interactions of caffeine and the adenosine system, these authors demonstrate that the effects of the adenosine analog R-N^6-phenylisopropyl-adenosine were not enhanced in caffeine tolerant subjects, suggesting that changes in central adenosine systems are not responsible for the tolerance that develops to the stimulant effects of caffeine.

Griffiths and Woodson review the literature on the reinforcing effects of caffeine from studies of laboratory animals and man. Their review shows that reinforcing effects of caffeine can be demonstrated in laboratory studies, however, these effects appear to be very weakly demonstrable in animals and, in addition, occur under limited conditions in man. These authors present some new information on the conditions under which the reinforcing effects of caffeine may be more robust. Those conditions appear to be those in which there is evidence of physiological dependence.

Katz *et al.* present data on behavioral effects of adenosine analogs and the interactions of those analogs with caffeine. Potency relations of the adenosine analogs suggest that their effects may be mediated by actions at A_2-adenosine receptors. The studies of the drugs in combination suggest that, while caffeine has antagonist actions at adenosine receptors, the behavioral stimulant effects of caffeine do not appear to be reversed by adenosine agonists, except at doses of the agonists that produce decreases in behavior when administered alone. These results do not support the notion that increases in rates of behavior, e.g., psychomotor-stimulant effects, produced by caffeine are due to its antagonist actions at adenosine receptors.

Finally, the paper by Williams and Jarvis presents information on potential therapeutic applications of methylxanthine related compounds, specifically drugs acting as adenosine-receptor antagonists. Such potential applications as antiasthmatic, nootropic, and cardiovascular system modulation, adenosine neuromodulation are discussed. Several non-xanthine adenosine antagonists, such as the pyrazolopyrimidine, DJB-KK, the pyrazoloquinoline, CGS 8216, and the pyrazolopyridine, etazolate, are examined. An exciting development is the pyrazoloquinazoline, CGS 15943A, the first potent non-xanthine A_2-selective antagonist. The evaluation of this compound may lead to the development of novel therapeutic agents as well as lead to a better understanding of the adenosine system.

Together these papers represent a summary of new results in this field as well as some review of previous studies. The symposium was organized by John M. Carney, with Drs. Carney and Jonathan L. Katz serving as symposium chairs, and in part sponsored by the Coffee Manufacturers Association and International Life Sciences.