Pharmacology Biochemistry & Behavior, Vol. 30, pp. 217–220. Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

INTRODUCTION

Progress in Understanding the Relationship Between the Pharmacological Effects of Nicotine and Human Tobacco Dependence

JACK E. HENNINGFIELD[1] AND STEVEN R. GOLDBERG

Addiction Research Center, National Institute on Drug Abuse, Baltimore, MD 21224

HENNINGFIELD, J. E. AND S. R. GOLDBERG. *Progress in understanding the relationship between the pharmacological effects of nicotine and human tobacco dependence.* PHARMACOL BIOCHEM BEHAV **30**(1) 217–220, 1988.—The present paper is intended to serve as an introduction to the series of eight papers which follow in this issue of *Pharmacology Biochemistry and Behavior*. A brief historical review of research that is at the root of much recent progress is provided in the present paper. In addition, we provide some data which illustrates the scope of tobacco-related research, world wide, in an effort to provide a perspective as to the vast amount of research activity that is currently in progress. Seven of the papers which follow were presented at a symposium held under the auspices of the American Society for Pharmacology and Therapeutics in 1986. Taken together, these papers are intended to provide new data and to review major areas of pharmacologic research relevant to the understanding and treatment of tobacco dependence. The topics include the behavioral and physiologic mechanisms by which the effects of nicotine are mediated, metabolic aspects of nicotine kinetics, and genetic determinants of responses to nicotine. The final paper is a discussion of the implications of these recent data for the pharmacologic treatment of tobacco dependence.

Cigarette smoking Tobacco Nicotine Drug dependence Treatment History Substance abuse

A symposium on the relationship between the pharmacological effects of nicotine and tobacco dependence was held under the auspices of the annual meeting of the American Society for Pharmacology and Therapeutics in 1986. The seven papers that comprised that symposium covered research topics including the pharmacologic basis of tobacco use, reinforcing and discriminative properties of nicotine, metabolism of nicotine, properties of brain nicotine receptors, genetic determinants of responses to nicotine, and the pharmacologic treatment of tobacco dependence. These papers, with the addition of one by Takada and his colleagues on discriminative properties of nicotine, are presented as a series in the present issue of *Pharmacology Biochemistry and Behavior*. Taken together, the papers are intended to represent recent areas of pharmacologic investigation that should lead to a better understanding of the biologic basis of the nicotine dependence process and its treatment. This introductory paper is intended to provide a historical and more general perspective from which to consider those that follow.

HISTORICAL NOTES ON STUDIES OF NICOTINE PHARMACOLOGY

Nicotine was first isolated from the leaves of tobacco (*Nicotiana tabacum*) in 1828, by Posselt and Reimanbasic. Since then, basic research on the pharmacologic actions of this alkaloid have contributed to basic findings on the functioning of the nervous system, as well as to the understanding of the biological basis of tobacco dependence [18,34]. For instance, the history of the study of ganglionic substances began with the studies of Langley and Dickinson [21], whose description of the functional effects of nicotine and other chemicals in autonomic ganglia led to Langley's proposal that interneronal transmission was chemically mediated. These studies lead to the initial postulation of "receptive substances" (viz. "receptor") that were responsible for the differential reactions of cells to various chemical activators [19]. Other work by Langley [20] and by Dixon [6] showed that nicotine's effects could be reduced by administration of ganglionic blockers (competitive blockade); that the magnitude of response to a given dose of nicotine was re-

[1]Requests for reprints should be addressed to Dr. Jack E. Henningfield, NIDA Addiction Research Center, P.O. Box 5180, Baltimore, MD 21224.

duced by pretreatment with nicotine (tolerance); and, that a few hours of time without nicotine administration was sufficient to restore responsiveness to nicotine.

Since Langley's classic work, neuropharmacologic research has turned to the characterization of central nicotinic receptors and to the identification of neurotransmitters involved in the mediation of nicotine's various behavioral and physiologic actions. Conceptual evolution from other areas of study have also affected research and theoretical analyses of tobacco-related phenomena. For instance, in the early 1970's, Martin and his colleagues proposed the notion that three distinct opioid activated receptor types were necessary to explain the diverse actions of the opioids [8,27]. Soon thereafter, research by Hughes, Kosterlitz, Goldstein and others lead to the identification of the receptive substrate itself (cf. [5]). Presently, these same strategies and technologies are being utilized to identify and characterize central nicoinic receptors (e.g., [1,28]).

The role of nicotine in the behavioral and physiologic responses produced by tobacco and in the self-administration of tobacco, have also had a long history that has benefitted and, in turn, benefitted from, opioid research. By the 1920's and 1930's, pharmacologists and other biomedical researchers, such as Lewin [26] and Armstrong-Jones [2], had concluded that nicotine was the primary pharmacologic factor to which the effects sought by tobacco users were due. During this era also, research on the possible effects of tobacco deprivation and administration on human performance began and although results were inconsistent, there was objective evidence that nicotine deprivation and administration, via the route of tobacco smoke inhalation, could produce significant behavioral effects (see individual data in [3]). Also, in the 1930's, Dorsey attempted to develop a substitution or replacement therapy using the ganglionic agonist lobeline as a replacement for tobacco delivered nicotine [7]. As will be reported in subsequent papers in the present series, lobeline is probably not an effective agonist for the critical central nicotine receptors [29], and it has not been found to be particularly efficacious in the treatment of tobacco dependence [15].

In 1942, Johnston concluded that tobacco use was essentially a means of delivering nicotine much as opium use was essentially a means of delivering morphine to the addicted person [17]. Early in the twentieth century, experimental quantification of the functional role of nicotine in tobacco dependence, however, was impeded by the absence of generally validated experimental models. Investigation of similar issues with opioids leads to the development of such models. For instance, studies with opioids in humans and animals lead to objective strategies to characterize tolerance, cross tolerance, physiologic dependence, production of transient discriminated effects (in humans, changes in mood and feeling state), and direct assessment of the reinforcing effects using self-administration procedures (cf. [10, 16, 31, 35]).

Using opioid generated models and other sophisticated research strategies, many, if not most, of the fundamental observations by the early researchers described above, have been verified and extended (see review, [11]). Other observations continue to provide a fruitful source of research direction as will be illustrated in the present series. For instance, whereas Lewin concluded that nicotine was an "excitant" (stimulant) [26], Armstrong-Jones concluded that the predominant action of nicotine was to sedate [2]. It is now apparent that nicotine, like most other psychoactive drugs, has diverse behavioral actions which depend upon the dose, the specific measure, the schedule of drug access, and so forth; thoroughly characterizing the stimulus properties of nicotine remains an active research topic [11,12]. Analogously, although research on the activity of nicotine at various receptor sites has been underway for nearly a century, progress on the role of specific sites and subpopulations of nicotine receptors in the mediation of tobacco dependence had been exceedingly slow until the last ten years. Finally, the implications of the pharmacodynamic properties of nicotine, including rapid gain and loss of neural tolerance, metabolism, and individual differences in such effects are only recently being systematically considered in the development of pharmacologic treatment strategies for tobacco dependence. Recent progress in each of the forementioned areas will be described in the present series of papers.

SCOPE OF TOBACCO-RELATED RESEARCH

Whereas progress is not necessarily a direct function of magnitude of effort, the magnitude of the world-wide tobacco/nicotine research effort is almost overwhelming. A few observations may provide some perspective. There are two readily available compendia of tobacco research. The first is the set of four volumes by Larson and his coworkers [22–25], in which more than 16,000 research reports are reviewed. The second is the abstracted Bibliobraphy of the U.S. Public Health Service, Office on Smoking and Health (OSH) (e.g., [32]). This reference file contains approximately 50,000 published papers, spanning almost two centuries of research and clinical observations. The majority of these reports, however, were published in only the last three decades.

A few additional facts about the OSH Bibliography illustrate why there is a continuing need for integrative symposia and series of papers such as the present. Since 1972, references have been added to the Bibliography at a rate of nearly 2,000 per year; most of these references were of new reports. Of these, there has been an average of appoximately 500 on the combined topics of "Pharmacology and Toxicology" and "Behavioral and Psychological Effects" of tobacco for each year from 1981 to 1985. During this time period, nearly 400 references were added pertaining to "Cessation" of cigarette smoking.

Since even this enormous bibliographic effort is not comprehensive, and since the range of topics of interest expanded (e.g., tobacco economics and policy issues have been increasingly monitored), such figures do not necessarily reflect specific research trends. Nonetheless, it is apparent that tobacco-related research is increasing in volume and scope, that behavioral and pharmacologic research is a significant portion of the total effort, and that there are no signs of imminent decline in tobacco research. In fact, it appears that new projects are being initiated at an increasing rate world wide [33].

The OSH also periodically assembles a Directory of Ongoing Research in Smoking and Health which is a compilation of current, on-going research being conducted throughout the world on smoking, tobacco, and tobacco use (e.g., [33]). The tenth edition of the Directory describes approximately 1,600 projects from 49 countries. The total number of projects represents a 45 percent increase over the number included in the preceding report (which summarized research ongoing in 1982). Thus, as rapidly as research findings have acrued in recent years, it is evident that the pace may be expected to continue to increase at least through the 1980's.

OVERVIEW OF THE PRESENT SERIES OF PAPERS

The present series of papers was selected in an effort to provide an overview of major topics included in current areas of pharmacologic research on tobacco dependence. The first paper of the series, by Henningfield and Goldberg [13], provides a brief description of some of the behavioral and pharmacologic determinants of compulsive tobacco use. The emphasis is on those factors which seem of relevance to the appreciation of the subsequent papers in the series.

The behavioral and physiologic mechanisms by which nicotine's effects are mediated will be discussed in greater detail in the subsequent papers in this issue. For instance, the characteristics of nicotine as a positive reinforcer for experimental animals and human subjects are reviewed and some recent data will be presented in the paper by Goldberg and Henningfield [9]. In addition to serving as reinforcers, drugs can control behavior by virtue of their discriminative stimulus properties; characterizing such properties permits comparison of the drug under study to other drugs, and thereby enhances understanding of the neurobiologic mechanisms by which the discriminative effects are mediated. The papers by Stolerman [29], and by Takada and his colleagues [30] present recent data from studies of the discriminative properties of nicotine compared to other drugs.

Insofar as both quantitative and qualitative aspects of the effects of a drug reflect the dose administered, pharmacokinetic factors are determinants in their own right. Rate of metabolism, in turn, is a determinant of nicotine pharmacokinetics that has received increasing study. Recent data from studies on the metabolism of nicotine by humans is the focus of the paper by Jacob and colleagues [14].

At the level of the central nervous system, it is presumed that the presence and functional characteristics of nicotine receptors can affect the range of responses likely to follow nicotine administration, as well the strength of those responses. The paper by Sloan and her colleagues [28] presents some of the data from their laboratory which indicate the presence of multiple nicotinic brain binding sites; it would appear that such sites are also of likely functional distinction. Two factors which are associated with the availability of brain nicotinic receptors are the genotype of the organism, and the level of sensitivity to nicotine of an organism prior to administration of nicotine. These factors are the subject of the paper by Collins and his colleagues [4].

The eight papers referred to above address basic behavioral and pharmacologic aspects of the control of behavior by nicotine. These papers also describe recent data concerning the neurobiologic mechanisms of nicotine action. These data, and other recently published data, have implications for the use of pharmacologic agents to assist in the treatment of tobacco dependence; this is the topic addressed by Jarvik and Henningfield [15] in the final paper in this series.

Taken together, this series of papers illustrates the breadth and distance of nicotine research since the pioneering observations of Langley. It is also evident that some of the basic questions themselves have changed. For instance, early questions such as the following are no longer the major impetus of research: "are the effects of nicotine related to dose?" "can nicotine serve as a reinforcer?" or, "are the effects of nicotine in the brain important in tobacco dependence? Rather, it is now more interesting to ask questions such as the following: "what are the functional properties of specific brain nicotine receptors?" "for which receptors could a selective agonist or antagonist be developed that would provide more effective means to control or eliminate tobacco dependence?" "what useful effects does nicotine serve which must be therapeutically addressed by means other than tobacco administration to facilitate abstinence and prevent relapse?"

Increasing sophistication in the questions asked, and further research should continue to provide a better understanding of the biological basis of tobacco dependence, the physiologic and behavioral consequences of tobacco use, and the most efficacious means of treatment for those who want to quit. The lines of research are several, however, and only time and further attempts to integrate various findings will tell which are most profitable. The main intent of this series of papers is to provide a reasonably state-of-the-art synthesis of current research related to the pharmacology of tobacco dependence.

REFERENCES

1. Abood, L. G., D. T. Reynolds, H. Booth and J. M. Bidlack. Sites and mechanisms of nicotine's action in the brain. *Neurosci Biobehav Rev* **5:** 479–486, 1981.
2. Armstrong-Jones, R. Tobacco, its use and abuse: From the nervous and mental aspect. *Practitioner* **118:** 6–19, 1927.
3. Bates, R. L. The effects of cigar and cigarette smoking on certain psychological and physiological functions: I dart throwing. *J Comp Psychol* **2:** 371–423, 1922.
4. Collins, A. C., L. L. Miner and M. J. Marks. Genetic influences on acute responses to nicotine and to nicotine tolerance in the mouse. *Pharmacol Biochem Behav* **30:** 269–278, 1988.
5. Cooper, J. R., F. E. Bloom and R. H. Roth. *The Biochemical Basis of Neuropharmacology*. New Oxford: Oxford University Press, 1978.
6. Dixon, W. E. The paralysis of nerve cells and nerve endings with special reference to the alkaloid apocodeine. *J Physiol* **30:** 97–131, 1903.
7. Dorsey, J. L. Control of the tobacco habit. *Ann Intern Med* **10:** 628–631, 1936.
8. Gilbert, P. E. and W. R. Martin. The effects of morphine- and nalorphine-like drugs in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. *J Pharmacol Exp Ther* **198:** 66–82, 1976.
9. Goldberg, S. R. and J. E. Henningfield. Reinforcing effects of nicotine in humans and experimental animals responding under intermittent schedules of IV drug injection. *Pharmacol Biochem Behav* **30:** 227–234, 1988.
10. Goldberg, S. R., R. D. Spealman and H. E. Shannon. Psychotropic effects of opioids and opioid antagonists. *Handbook Exp Pharmacol* **55:** 269–304, 1981.
11. Henningfield, J. E. Behavioral pharmacology of cigarette smoking. In: *Advances in Behavioral Pharmacology, Vol IV*, edited by T. Thompson and P. B. Dews. New York: Academic Press, 1984, pp. 131–210.
12. Henningfield, J. E. and S. R. Goldberg. Stimulus properties of nicotine in animals and human volunteers: A review. In: *Behavioral Pharmacology: The Current Status*, edited by R. L. Balster and L. S. Seiden. New York: A. R. Liss, 1984, pp. 433–449.
13. Henningfield, J. E. and S. R. Goldberg. Pharmacologic determinants of tobacco self-administration by humans. *Pharmacol Biochem Behav* **30:** 221–226, 1988.
14. Jacob, P., III, N. L. Benowitz and A. T. Shulgin. Recent studies of nicotine metabolism in humans. *Pharmacol Biochem Behav* **30:** 249–253, 1988.

15. Jarvik, M. E. and J. E. Henningfield. Pharmacological treatment of tobacco dependence. *Pharmacol Biochem Behav* **30:** 279–294, 1988.
16. Jasinski, D. R. Assessment of abuse potentially of morphinelike drugs (methods used in man). In: *Handbook of Experimental Pharmacology*, edited by W. R. Martin. Berlin: Springer-Verlag, 1977, pp. 197–258.
17. Johnston, L. M. Tobacco smoking and nicotine. *Lancet* **2:** 742, 1942.
18. Kharkevich, D. A. Introduction. In: *Pharmacology of Ganglionic Transmission*, edited by D. A. Kharkevich. Berlin: Springer-Verlag, 1980, pp. 1–8.
19. Langley, J. N. On the reaction of cells and of nerve-endings to certain poisons, chiefly as regards to the reaction of striated muscle to nicotine and to curari. *J Physiol* **33:** 374–413, 1905.
20. Langley, J. N. The antagonism of curari and nicotine in skeletal muscle. *J Physiol* **48:** 73–108, 1914.
21. Langley, J. N. and W. L. Dickinson. On the local paralysis of the peripheral ganglia and on the connexion of different classes of nerve fibres with them. *Proc R Soc Lond* **46:** 423–431, 1889.
22. Larson, P. S., H. B. Haag and H. Silvette. *Tobacco, Experimental and Clinical Studies. A Comprehensive Account of the World Literature*. Baltimore: Williams and Wilkins, Co., 1961.
23. Larson, P. S. and H. Silvette. *Tobacco, Experimental and Clinical Studies. A Comprehensive Account of the World Literature, Supplement I*. Baltimore: Williams and Wilkins, Co., 1968.
24. Larson, P. S. and H. Silvette. *Tobacco. Experimental and Clinical Studies. A Comprehensive Account of the World Literature, Supplement II*. Baltimore: Williams and Wilkins, Co., 1971.
25. Larson, P. S. and H. Silvette. *Tobacco. Experimental and Clinical Studies. A Comprehensive Account of the World Literature, Supplement III*. Baltimore: Williams and Wilkins, Co., 1974.
26. Lewin, L. *Phantastica: Narcotic and Stimulating Drugs: Their Use and Abuse*. London: Kegan Paul and Trench, Ltd., 1931.
27. Martin, W. R., C. G. Eades, J. A. Thompson, R. E. Huppler and P. E. Gilbert. The effects of morphine- and nalorphine-like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther* **197:** 517–532, 1976.
28. Sloan, J. W., W. R. Martin, M. Bostwick, R. Hook and E. Wala. The comparative binding characteristics of nicotinic ligands and their pharmacology. *Pharmacol Biochem Behav* **30:** 255–267, 1988.
29. Stolerman, I. P. Characterization of central nicotinic receptors by studies on the nicotine cue and conditioned taste aversion in rats. *Pharmacol Biochem Behav* **30:** 235–242, 1988.
30. Takada, K., T. J. Hagen, J. M. Cook, S. R. Goldberg and J. L. Katz. Discriminative stimulus effects of intravenous nicotine in squirrel monkeys. *Pharmacol Biochem Behav* **30:** 243–247, 1988.
31. Thompson, T. and K. R. Unna (Eds.). *Predicting Dependence Liability of Stimulant and Depressant Drugs*. Baltimore: University Park Press, 1977.
32. U.S. Department of Health and Human Services, Office on Smoking and Health, *1985 Bibliography on Smoking and Health*. Washington, DC: U.S. Government Printing Office, 1986.
33. U.S. Department of Health and Human Services, Office on Smoking and Health. *1984–1985 Directory, On-Going Research in Smoking and Health*. Washington, DC: U.S. Government Printing Office, 1985.
34. Volle, R. L. Nicotinic ganglion-stimulating agents. *Pharmacol Ganglion Transm* **9:** 281–307, 1980.
35. Woolverton, W. L. and C. R. Schuster. Behavioral and pharmacological aspects of opioid dependence: Mixed agonist-antagonists. *Pharmacol Rev* **35:** 33–50, 1983.