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Pharmacologic Determinants of Tobacco Self-Administration by Humans

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HENNINGFIELD, J. E. AND S. R. GOLDBERG. *Pharmacologic determinants of tobacco self-administration by humans.* PHARMACOL BIOCHEM BEHAV **30**(1) 221–226, 1988.—Tobacco is a naturally occurring source of nicotine, which is a chemical of demonstrable abuse liability and dependence potential. All commonly used forms of tobacco result in the delivery of nicotine to the central nervous system (CNS), where its actions affect the probability of subsequent use. The role of nicotine as a determinant of patterns of tobacco self-administration and other tobacco-associated responses has frequently been confounded by the complexity of this form of drug self-administration, since the amount of nicotine delivered to the CNS is not a simple function of the amount of tobacco consumed. The present paper is a summary of data which indicate that nicotine administration and withdrawal are determinants of tobacco ingestion. Recent data that are reviewed include those which indicate that the following effects of nicotine bear an orderly relation to the dose administered: (1) reduction of cigarette smoking, (2) production of discriminative effects, and (3) blockade of tobacco withdrawal symptoms. A secondary intent of the present paper is to describe aspects of tobacco dependence which are relevant to the appreciation of the subsequent papers appearing in this series of eight.

Tobacco Cigarette smoking Drug abuse Drug dependence Tolerance Withdrawal Performance

IN the 1920's and 1930's, the scientific evidence was sufficient to lead prominent pharmacologists and clinicians to conclude that nicotine was primary pharmacologic agent obtained through the use of tobacco which was responsible for the effects sought by tobacco users [2, 40 42]. Since then, a considerable amount of research has been conducted to investigate the specific functional role of nicotine in tobacco (cf. reviews, [16, 21, 53, 54]), and the actions of nictone in the brain [1,4].

One specific area of considerable research effort was to determine the role of nicotine dose level in rate of tobacco self-administration. Although the conclusion of most reviewers was that nicotine dose level was a determinant of cigarette smoking behavior [16, 21, 54], the apparent weakness of the relationship was sometimes taken as a reflection of the lack of importance of nicotine as a determinant of tobacco intake. Such observations were difficult to reconcile with others such as the widely observed difficulty in substituting nonnicotine delivering substances for tobacco by users [16,54]. In retrospect, it has become apparent that many studies in which an effort was made to determine the relation between nicotine dose and subsequent behavior used rather ineffective and poorly controlled means to vary nicotine delivery (e.g., cigarette brand switching), and/or measured dependent variables that do not necessarily reflect actual tobacco intake (e.g., number of cigarettes smoked) (see critique of "titration" studies, [21]). More recently, several strategies have been used to evaluate the functional properties of nicotine dose manipulations as a determinant of tobacco smoking and withdrawal. Some of these data will be summarized in the present paper.

TOBACCO USE: AN ORDERLY BEHAVIOR PHARMACOLOGIC PROCESS

Tobacco self-administration has been recognized as a pharmacologically mediated behavior by scholars of nearly four centuries who have described various medicinal and "psychic" benefits of smoking and debated its adverse effects [3]. Beginning most actively in the 1970's, the same strategies used to study self-administration of other drugs was applied to the study of tobacco and nicotine self-administration by animal and human research subjects (cf. review, [21]). These studies revealed the behavior to be an orderly form of drug self-administration that was contolled by the same kinds of variables that control other forms of drug self-administration. These controlling variables will be summarized below.

Tobacco Use is a Complex Form of Nicotine Self-Administration

Nicotine is the only chemical available in biologically significant quantity in tobacco that has been shown to meet criteria for an abusable drug. Specifically, in the absence of tobacco, nicotine produces dose-related centrally-mediated discriminative effects in animal and human subjects (cf. review, [26]); nicotine produces positive dose-related elevations of scores on drug liking scales and on the Morphine

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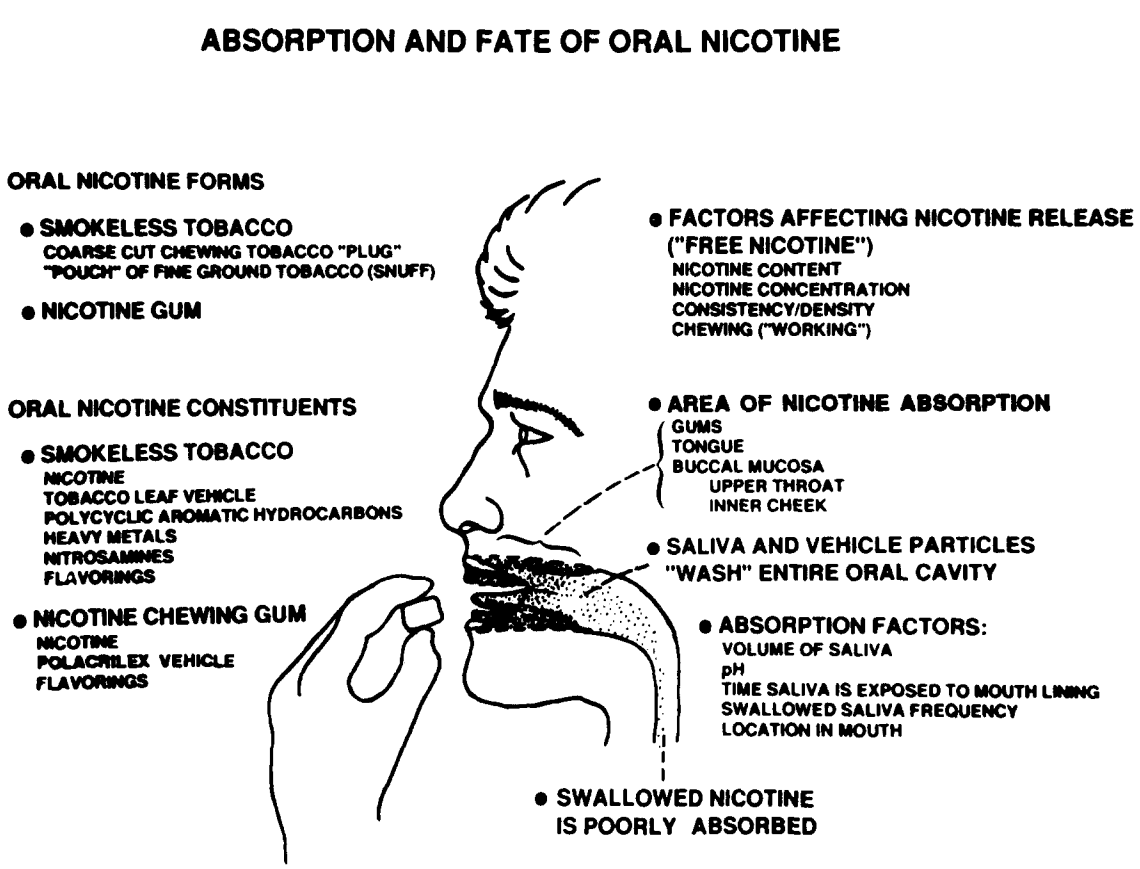

FIG. 1. This figure shows some of the factors which affect the amount of nicotine extracted and absorbed from smokeless tobacco and nicotine gum. As suggested by the figure, the systemic nicotine dose is only partially related to the amount of nicotine in the formulation. Other factors, such as oral pH and time of exposure of nicotine to the buccal mucusa (limited by swallowing or expectoration), are also determinants of nicotine absorption. Other factors, such as amount of mechanical activity ("working" or "chewing") required to physically extract the nicotine from the vehicle, may be significant determinants of nicotine extraction from the gum formulation but appear to be weaker determinants of nicotine extraction from smokeless tobacco products.

Benzedrine Group ("MBG" or "Euphoriant") scale in volunteers with drug abuse histories [33]; nicotine is a positive reinforcer for animal and human subjects (cf. review, [10]). These data indicate that nicotine meets the same criteria for a drug with a liability for abuse, or potential to produce dependence, as do other dependence-producing drugs. The reinforcing efficacy of nicotine can be further enhanced by its possibly individual- or situation-specific useful effects (e.g., performance enhancement, weight reduction) [9,63]. Finally, as discussed further on, repeated administrations of nicotine, like some drugs of abuse, can produce a state of physiologic dependence which may enhance its reinforcing efficacy during abstinence.

Tobacco, as is typically processed and used, is an efficient means of nicotine delivery which not only provides a stable and readily available nicotine source, but also permits the individual to regulate nicotine intake [21]. A typical commercially produced cigarette contains approximately 10 mg of nicotine of which approximately 1 mg is typically extracted per cigarette [6,11]. As the large excess amount of potentially available nicotine would imply, the actual amount obtained per cigarette varies widely across individuals, and varies somewhat across cigarette type, however, the main determinant of nicotine intake appears to be how the cigarettes are smoked (e.g., [39]). The complexity of the process by which the cigarette is combusted, tar and gasses are produced, nicotine is vaporized, and some of the resultant particulate matter and vapor are inhaled, has been described and illustrated [21,22].

Increasing attention has recently been paid to the process by which nicotine is extracted and absorbed from smokeless tobacco products and from nicotine delivering polacrilex resin (gum). A schematic illustration of this process is shown in Fig. 1. Nicotine extraction from the gum is highly dependent upon active mechanical effort (chewing or "working"), a feature that discourages unintended nicotine self-administration (e.g., by children) but can also prevent proper self-medication in persons who have not received proper instructions [36].

It would appear that the process of nicotine extraction from smokeless tobacco products can be somewhat affected by mechanical oral activity, however, the ground or cut tobacco leaf appears to provide a vehicle from which nicotine extraction is less dependent upon instructions or experience [30]; therefore smokeless tobacco users can probably make greater adjustments in their nicotine dose by varying the amount of product they use over time and the strength (nicotine concentration) of that product. In addition, since

the amount of nicotine extracted from a given quantity is a function of the nicotine concentration, and since absorption is directly related to pH, manufacturers can, and have, controlled the pH and nicotine concentration of products so as to provide a graduated series to faciliate establishment of the drug seeking behavior [30]. This is similar to strategies used to establish drug self-administration in laboratory animals with nicotine and with other drugs in which low "primary" doses are often used to establish the behavior of drug self-administration (e.g., [10, 44, 66]).

Patterns of Tobacco Self-Administration are Regular

Following initial exposure to tobacco, acquisition of cigarette smoking and smokeless tobacco use occurs gradually, in most people, over a period of several years [23]. This pattern is likely to be related to the development of tolerance since saliva thiocyanate levels (a correlative measure on nicotine intake) also increase as age of the smokers increases, even when cigarette intake is held constant [51]. After several years of smoking cigarettes, however, nicotine intake is relatively stable from day to day, and changes in product supply or type are met with compensatory changes in nicotine intake [5,54]. Within each day, there is a tendency to smoke most heavily upon initial waking; however, the rest of the day is characterized by monotonic patterns which are maintained even if total supply of cigarettes is limited [13]. Within each cigarette, as well, the pattern of puffing is orderly: rate of puffing and duration of each puff decrease across subsequent puffs on the cigarette [13, 45–48].

Patterns of Tobacco Self-Administration are Related to Tobacco Dose

When the concentration of tobacco smoke is reduced by increasing the ventilation using preforated cigarette holders [28,60], more cigarettes tend to be smoked and more puffs taken per cigarette (cf. reviews, [16,21]). Analogously, if the number of puffs permitted per cigarette smoking bout are decreased, the number of smoking bouts increases, and vice versa [15]. Conversely, if the interval between bouts is increased, the number of puffs taken per bout also increases, and vice versa [15]. Such compensatory changes in self-administration are not perfectly related to tobacco dose; as unit dose increases, total amount obtained increases as well, but not as much as would have occurred had there been no compensatory change [16,21]. This is similar to the effects of dose manipulations in when other drugs serve as reinforcers and for other species [12, 31, 66].

Tobacco Deprivation Affects Latency to Smoke

The time to light and smoke a cigarette from the moment of its availability is inversely related to the time since the last cigarette [29]. That, at least, partial control of this relationship is specific to nicotine is suggested by studies in which nicotine gum pretreatment increases the latency to smoke in a fashion that is directly related to the nicotine dose of the gum [50].

Nicotine Affects Cigarette Smoking

The preponderance of evidence from studies of the functional role of nicotine in cigarette smoking has led to the conclusion that increasing nicotine dose levels are associated with decreases in cigarette smoking and vice versa [14, 16, 21]. The following kinds of studies have lead to this conclusion: variation of nicotine dose per cigarette leads to compensatory changes in smoking (e.g., [56]); variation of urine pH (increasing urinary pH increases rate of excretion of nicotine) leads to compensatory changes in smoking [7]; centrally and peripherally blocking ganglionic drugs produce the same effect as an abrupt decrease in nicotine dose [49, 52, 59], but a noncentrally acting nicotine blocker had no such effect [59]; administration of nicotine by other routes (e.g., oral, intravenous) results in decreased cigarette smoking [32,50]. These compensatory changes in cigarette smoking or nicotine intake are far from perfect, as is the case with other abused drugs (cf. [12,31]). Thus, increasing the unit dose results in decreased doses taken but and increase in overall nicotine intake; the converse is also true [16,21].

Interestingly, as Russell has observed, it appears that people are more sensitive to increases in nicotine dose than they are to decreases, possibly because the aversive effects of increased doses have a more immediate effect on self-administration behavior [55]. Alternatively, since few such studies of the role of nicotine dose on cigarette intake employed sophisticated measures of smoking behavior (e.g., puff volume or even puffs taken) or resultant nicotine intake (e.g., plasma nicotine or cotinine), it is possible that decreasing dose levels of cigarette are compensated by frequently unmeasured changes in within cigarette parameters of puffing and inhaling.

PHYSICAL DEPENDENCE POTENTIAL OF NICOTINE

As measures of abuse liability assessment indicate the ability of a drug to take control over the behavior of one who is exposed to it, so measures of physical dependence potential provide an indication of the ability of a drug to produce a state of physiologic dependence. Physiologic dependence can increase the behavioral control exerted by a drug by providing a means of enhancing its reinforcing efficacy. Inextricably involved in the development of physiologic dependence to a drug is the tolerance which develops following repeated exposure. Since tolerance develops differentially across response measures, it may appear virtually complete on some measures (e.g., the pleasant subjective effects of nicotine), and partial on other measures (e.g., changes in heartrate). Similarly, whereas some tolerance may persist for years beyond the termination of tobacco use, some degree of tolerance is lost within a few hours of the last cigarette [38]. The consequence of this is that every morning, for a few cigarettes at least, it is possible to reexperience the subjective satisfaction incurred by nicotine administration. Later during the day, cigarettes are often described as being "smoked out of habit" or "to avoid discomfort and craving," but not necessarily because they continue to provide substantial pleasure in their own right. In fact, like the opioids, once tolerant, the person may report needing the drug simply to sustain feelings of "normalcy."

Nicotine has been suspected to produce physiologic dependence for several decades [53,54], and active study of such a possibility began in the 1970's [57]. It has only been in recent years, however, that the same strategies used to assess withdrawal from opioids and sedatives have been rigorously extended to study the withdrawal from tobacco. The most comprehensive series of such studies have been those of Hughes and Hatsukami and their co-workers [18–20, 34, 35]. Taken together the findings of these studies include the following: (1) abrupt abstinence from nicotine delivered via

tobacco smoke, nicotine gum, and smokeless tobacco (chewing tobacco), leads to qualitatively similar syndromes; (2) the nicotine abstinence syndrome includes decreased heartrate, and increased anxiety, irritability and desire to smoke (weight gain also occurs but other data suggest that this may simply represent the removal of the apparently robust weight reducing effects of nicotine (cf. reviews, [8,17]); (3) withdrawal symptoms occurring when nicotine gum use is terminated appear less likely to be accompanied by relapse to nicotine self-administration than when tobacco product use is terminated [18–20, 34–36]. Recent studies by West and his co-workers, and by Henningfield and his co-workers, have verified and extended those summarized above [27, 64, 65].

An interesting finding that has emerged from studies by Henningfield and his co-workers is that nicotine administration in the form of nicotine gum effectively blocks physiologic and behavioral markers of tobacco withdrawal under conditions in which the gum is not rated as being "liked" nor blocking the "desire to smoke" (unpublished data). For instance, in one study, 12 hours of tobacco deprivation produced reliable decrements in ability to perform on a computerized test battery (including measures such as rapid arithmetic and logical reasoning); these impairments were reversed by the chewing of nicotine delivering gum. Other preliminary finding from this series of studies were that certain behavioral and physiological parameters of withdrawal did not recover after 10 days of abstinence, suggesting the possibility that the withdrawal process may persist for an indefinite amount of time.

Finally, even though urge to smoke is a reliable indicator of early withdrawal, it is not a specific indicator (see also, [64]), and in the study described above, urge did not systematically vary as function of nicotine administration. Such urges are apparently evoked by stimuli formerly associated with smoking; the consequence of this is that nicotine administration can alleviate one condition which elicits the urge to smoke, i.e., tobacco withdrawal, but does not selectively reduce this response (cf. [24,25]); therefore, the overall affect of nicotine gum on the urge to smoke is weak at best, and not significant in most studies [36].

There are some clinical implications of experimental studies of tobacco withdrawal. The first is that most people who are struggling to quit smoking have been smoking for many years and so it is not clear what their baseline, nonsmoking physiologic and behavioral levels of functioning are. Moreover, since most cigarette smokers began smoking in their adolescent years during hormonal and other development, administration of nicotine itself, may have affected the course of their physiologic and behavioral development. For instance, decreased heartrate is a reliable physiologic correlate of tobacco abstinence [34]. Following termination of smoking, heartrate appears to stabilize at some level lower than that which was chronically elevated by nicotine administration and higher than that observed during the first week following the termination of cigarette smoking (unpublished data from Henningfield). Thus, it may not be meaningful to ask what the "true" baseline heartrate should be when abstinence follows many years of smoking including during years of marked behavioral and physiological development.

Another implication of recent data is that it may be difficult to distinguish effects due to physical dependence from the emergence of signs and symptoms that had been chronically suppressed ("treated") by nicotine administration. For instance, to what degree is the abstinence related anxiety observed in some people a rebound effect of anxiolytic properties of nicotine and to what degree is it the emergence of symptoms in an anxiety-prone individual which were suppressed by chronic nicotine administration? Similarly, the effects of nicotine on weight, and possibly other measures, appear to be chronic and robust, such that tobacco abstinence results in remarkably consistent elevations in weight; this suggests the possibility that weight gain may not be appropriately categorized a nicotine withdrawal effect (see also [17]). Regardless of the underlying mechanism of action, however, these signs and symptoms, together, provide the basis for distinguishing to nicotine withdrawal syndrome [36].

CONCLUSIONS

As this brief review has shown, nicotine is a critical determinant of tobacco associated phenonmena (including self-administration and physiologic dependence) [61,62]. This is not to imply that it is the only factor; all forms of drug addiction involve a variety of social, individual, and environmental determinants other than the actions of the drug in the central nervous system [41]. It is clear, however, that researchers in the earlier portion of this century were correct in their conclusions that the role of nicotine in the behavior of tobacco ingestion was the same as the role of morphine in the ingestion of opium-derived products [37]. Specifically, repeated nicotine administration leads to tolerance, physiologic dependence, and dependence of "normal," "comfortable" behavioral functioning upon its regular daily ingestion. Patterns of nicotine ingestion are not capricious but rather are orderly and related to factors such as nicotine dose and time since the last ingestion. Finally, environmental stimuli associated with the effects of nicotine administration and withdrawal appear to function as do stimuli associated with the use of other addicting drugs (e.g., as determinants of urges to self-administer).

It may also be concluded that the naturally occurring tobacco vehicles for nicotine delivery are not necessary to enable nicotine to produce discriminated interoceptive effects, and physiologic and behavioral control. The tobacco vehicle does provide three practical benefits to tobacco product manufacturers: (1) it provides exemption from oversite by the Food and Drug Administration, and (2) it provides an ideal confluence of stimulus properties, and (3) it provides a controllable system of nicotine bioavailability that optimizes the potential of nicotine to modify behavior. The latter consideration would currently seem of lesser importance since current manufacturing techniques and resources make plausible the possibility that nontobacco nicotine-delivering products could be developed that would be highly satisfactory substitutes for tobacco. Since it is the tobacco vehicle that is the primary source of disease and mortality that are consequent to nicotine dependence, such products might seem, at first consideration, to be desirable. However, it is possible that such products would also be of similar potential for establishment and maintenance of nicotine addiction, as are tobacco products. It would follow, from these observations, that such attempts at development and marketing of nonconventional nicotine delivering products should be subject to the same sorts of testing as are psychoactive drugs in general, as was the currently available nontobacco nicotine delivering formulation (nicotine polacrilex gum).

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