Chapter 7

Pharmacology and Toxicology of Nicotine

Contents

Figure

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GENERAL PHARMACOLOGIC ACTION OF NICOTINE ON NERVE CELLS

The pharmacology and chronic toxicity of nicotine, in dosage comparable to the amounts that man may absorb from smoking or other use of tobacco, are pertinent to an evaluation of health hazard.

The most notable action of nicotine involves a direct effect on sympathetic and parasympathetic ganglion cells (18). This usually occurs as a transient excitation, followed by depression, or even paralysis with effective doses, The ganglia are rendered more sensitive to acetylcholine initially and thus make preganglionic impulses more effective. Paralysis is associated with diminished sensitivity of ganglia to acetylcholine and concomitant reduction in the intensity of postganglionic discharges. Similar effects occur at the neuromuscular junction, resulting in a curariform action in skeletal muscle with adequate doses (16). In the central nervous system, as in ganglia, primary stimulation is succeeded by depression. Furthermore, nicotine like acetylcholine discharges epinephrine from the adrenal glands and other chromaffin tissue (20); it also releases antidiuretic hormone from the posterior pituitary by stimulating the supraopticohypophyseal system (3). Nicotine also augments various reflexes by excitation of chemoreceptors in the carotid body (10)

The pharmacological response of the whole organism at any one time therefore, representing as it does the algebraic sum of stimulant and depressant effects resulting from many direct, reflex, and chemical mediator influences on autonomic nervous transmission and excitability of virtually all organ systems, defies accurate description. The wide variation in smoking habits leads to every conceivable pattern of fluctuating blood levels of nicotine during the day. This suggests strongly that nicotine-sensitive cells may be shifting continuously from excitation to depression. Such activity probably accounts for the unpredictable effects observed in different individuals and in the same individual at different times. Using the classic pharmacological approach, it is therefore virtually impossible to make reliable statements regarding the effect of smoking on the many organ systems. In order to characterize the biological effects of nicotine in man, it thus becomes necessary to place heavy reliance on symptoms and signs derived from clinical and epidemiological studies.

EFFECTS ON THE CENTRAL NERVOUS SYSTEM

The action of nicotine on central nervous system functions has recently been reviewed (20). Very little of the reported work involves human

experimentation, and most of it is with doses much larger than are associated with the act of smoking. It suffices to note here that moderate doses of nicotine elicit marked increases in respiratory, vasomotor, and emetic activity, and still larger doses lead to tremors and convulsions, both in animals and man. The amounts absorbed even in heavy smoking may produce transient hyperpnea through carotid and aortic arch reflexes (5). The increase in blood pressure which is commonly observed is partly central in origin. Nausea and emesis are more pronounced in the novice smoker but may occur even in heavy smokers with excessive use of tobacco. Electroencephalographic (EEG) studies in the intact rabbit (21) indicate that nicotine, in doses of 0.5 to 3.0 milligrams per kilogram, produced an "arousal reaction" involving the hippocampus. In a later stage of the same reaction there appeared a discharge pattern similar to that noted in convulsions. Lesions in the septum abolished the "arousal reaction," chlorpromazine and evipan abolished the discharge pattern. None of the congeners of nicotine, including lobeline, produced similar patterns.

Knapp and Domino (12) found that concentrations of nicotine (10 to 20 μg/kg), a level commonly reached in man by smoking, produced EEG arousal patterns in four species of animals, the rabbit, cat, dog, and monkey, after neopontine transection. These effects did not appear to be related to fluctuations in blood pressure or to catecholamine or serotonin levels.

In a study of electrical activity (as measured by electroencephalogram) in 25 human subjects before and after smoking one cigarette, Lambiase and Serra (15) noted an 80 percent depression in voltage and an acceleration in frequency of the alpha rhythm which remained unchanged in form during the recordings. These alterations were more consistent in subjects over 35 years of age and were attributed to carbon monoxide and nicotine resulting in cerebral anoxia and/or release of epinephrine. Hauser et al. (9), who studied the EEG changes on cigarette smoking in healthy young adults, obtained highly variable responses usually toward an increase in the dominant alpha frequency of 1 or 2 cycles per second. Some subjects showed similar changes when puffing a glass cigarette stuffed with cotton and others when puffing specially prepared nicotine-free cigarettes. They concluded that the effects noted were more likely to represent a psycho-physiologic response to the act of smoking than to any substances present in cigarette smoking. Bickford (1) arrived at a similar conclusion. Wide gaps of information exist in this area and it is not meaningful to attempt inferences concerning correlations of electrical events in the central nervous system and subjective effects of smoking from the type of evidence currently available.

CARDIOVASCULAR EFFECTS

The cardiovascular effects of nicotine are described in Chapter 11, Cardiovascular Diseases.

GASTROINTESTINAL EFFECTS

Most but not all experimental and clinical evidence supports the popular view that smoking reduces appetite (6, 17 p. 271). This reduction has been attributed both to direct effects on gastric secretions and motility and to reflexes arising from local effects on the taste buds and mucous membranes in the mouth. The unpredictable and temporary elevation of blood sugar is probably too small to contribute significantly (17, p. 326). Nicotine effects on the hypothalamus, comparable to the appetite reduction produced by other stimulants like amphetamine, and psychological mechanisms may play significant roles (23). Hunger contractions are inhibited but gastric movements of digestion do not appear to be influenced significantly by moderate smoking (4).

Nausea, often associated with vomiting, is by far the most common symptom related to the gastrointestinal tract. This effect probably originates centrally in the medullary emetic chemoreceptor trigger zone (14). It is now generally agreed that nicotine stimulates peristalsis but the mechanism is a complex one, probably involving local, central and reflex actions. Schnedorf and Ivy (21) found wide individual variation in gastrointestinal passage time in medical student smokers and non-smokers but gained the impression that smoking tends to augment motility of the colon. These effects are probably related to actions on the parasympathetic ganglia in the bowel. The summative effects of all of these pharmacological actions on the whole intestinal tract do not produce a consistent pattern. Excessive smoking may be associated with diarrhea, constipation, or alternating patterns between the two extremes. The only consistency is that symptoms attributable to nicotine effects on the gastrointestinal tract are very common.

DISTRIBUTION AND FATE

Nicotine is actively and rapidly metabolized by man and other mammals, the metabolites being in large measure excreted in the urine. If any tissue storage occurs, it is in such small quantity as to elude current analytical technics. Nicotine is a rather unstable molecule which in neutral or alkaline conditions undergoes a variety of changes. A review of the current concepts of the known and suggested pathways for the metabolism of nicotine is shown in Figure 1 (18). The main intermediate appears to be (—)-cotenine which yields γ-(3-pyridyl)-γ-methylamino butyric acid. Cotenine has low toxicity and lacks the potent pressor activity of nicotine.

Dogs receiving 150 mg/kg/day orally for 108 days exhibited no weight loss or other objective signs (2). Man has ingested 500 mg orally at 8-hour intervals for 6 days without untoward effects. No evidence has been presented that the other known metabolites of nicotine carry any significant systemic toxicity.

SUMMARY DIAGRAM OF ROUTES FOR THE METABOLISM OF NICOTINE IN MAMMALS

(Some hypothetical intermediates are shown in brackets.)

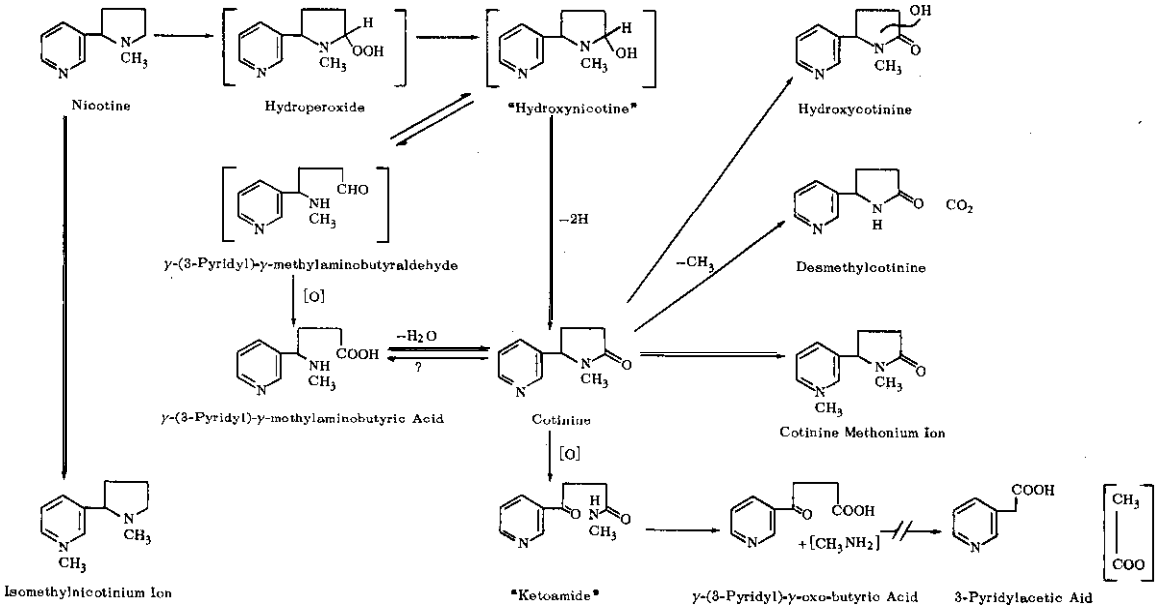

FIGURE 1.

Source: McKennis, Herbert H., Jr. (18)

CHRONIC TOXICITY

Evaluation of the chronic toxicity of tobacco smoke may be considered in several categories: (a) the systemic toxicity of nicotine or its congeners, (b) the systemic toxicity of other constituents of smoke or tobacco, carbon monoxide and other compounds, (c) specific organ toxicity in certain susceptible individuals. such as those with Buerger's disease and allergic responses, (d) local effect of irritants on mucous and pulmonary membranes by tars, phenols, the oxides of nitrogen, and others. The latter three types of potential toxicity are discussed in Chapter 9, Cancer, and Chapter 10, Non-Neoplastic Respiratory Diseases.

It might appear that the least difficult problem in this group of variables would be to assess the chronic toxicity of nicotine since we are dealing with a comparatively simple organic compound of known composition and reaction. Whereas there is a voluminous literature of studies involving chronic exposure to nicotine or tobacco smoke in many animal species (17, pp. 501-504), most of these are poorly designed and controlled and are of little value for extrapolation to man. For example, in the best nicotine experiments involving life span studies, the daily dose of nicotine was near the maximal tolerated dose (just subconvulsive), which is greatly in excess of any human smoking exposure. Even though some authors (11) observed weight loss and degenerative vascular changes in rats under these severe conditions, others (22) noted some weight loss but no histologic change. In life span experiments in rats, with tobacco smoke in amounts approximating human smoking exposure, very little systemic toxicity was noted (8, 13). Even though animal experimentation is inadequate, especially in long-term effects of nicotine on large animal species, existing data permits a tentative conclusion that the chronic systemic toxicity of nicotine is quite low in small to moderate dosage.

The clinical literature is devoid of human data concerning chronic exposure to nicotine alone, and the general statements regarding the chronic toxicity of nicotine for man represent inferences drawn from chronic exposure to tobacco in various forms, including industrial poisoning. Repeated exposure to tobacco in excessive amounts is reported to induce amblyopia, arrhythmias, digestive disturbances, cachexia and a wide variety of other signs and symptoms. But the effects of excessive dose are of little concern here. The question is whether prolonged *exposure to nicotine,* in the quantities absorbed systemically from smoking or other tobacco use, produces toxic effects which result in unpleasant symptoms, dangerous signs, specific degenerative disease, or shortening of the life span. Unfortunately even a tentative answer to this question must be obtained indirectly and by making certain assumptions. Inasmuch as nicotine is systemically absorbed from all routes of administration, smoking, chewing, snuffing, or "snuff dipping,"* it appears logical to assume that if the amounts of nicotine absorbed in the various methods of use are of the same order of magnitude, any toxic effects observed should also be in this order of magnitude. There appears to be general agreement that this is so. Calculations indicate that the nicotine

*A small amount of snuff is placed in the groove between the teeth and the lower lip or beneath the tongue and held there from 30 minutes to several hours.

absorbed (40-60 mg) from 6 cigars uninhaled equals that from 30 cigarettes inhaled (19). Chewing tobacco may yield 8 to 87 mg in 6 to 8 hours (24); in chewing snuff, 20-60 mg of nicotine (7).

The following variables play a role in the amount of nicotine absorbed (17, p. 8):

> To sum up, the rate and amount of absorption of nicotine by the smoker depend to a greater or less extent upon the following factors:
>
> 1. Length of time the smoke remains in contact with the mucous membranes;
> 2. pH of the body fluids with which the smoke comes in contact:
> 3. Degree and depth of inhalation;
> 4. Degree of habituation of the smoker (?);
> 5. Nicotine content of the tobacco smoked;
> 6. Moisture content of the tobacco smoked;
> 7. Form in which tobacco is smoked (cut [cigarettes] or uncut [cigars]) (?);
> 8. Length of butt;
> 9. Use of holder or filter;
> 10. Alkalinity or acidity of the tobacco smoke (?);
> 11. Agglomeration of smoke particles (more important in cigarette-smoking).

There is no acceptable evidence that prolonged exposure to nicotine creates either *dangerous* functional change of an objective nature or degenerative disease. The minor evidences of toxicity, nausea, digestive disturbances and the like, are similar in kind and degree with all forms of use.

The fact that the over-all death rates of pipe and cigar smokers show little if any increase over non-smokers is very difficult to reconcile with a concept of high nicotine toxicity. In view of the mortality ratios of pipe and cigar smokers, it follows logically that the apparent increase in morbidity and mortality among cigarette smokers relates to exposure to substances in smoke other than nicotine. Unfortunately, there are no useful mortality statistics in those who chew, snuff, or "dip" tobacco, and the literature regarding industrial exposure is so confusing that little help is available here. The type of projection made above, however unsatisfactory, is not inconsistent with the animal toxicity data as well as the fact that nicotine undergoes very rapid metabolism to substances of low toxicity. The evidence therefore supports a conclusion that the chronic toxicity of nicotine in amounts ordinarily obtained in common forms of tobacco use is very low indeed.

SUMMARY

The pharmacological effects of nicotine at dosage levels absorbed from smoking (l–2 mg per inhaled cigarette) are comparatively small; the response in any point in time represents the algebraic sum of stimulant and depressant actions from direct, reflex, and chemical mediator influences on the several organ systems. The predominant actions are central stimulation and/or tranquilization which vary with the individual, transient hyperpnea,

peripheral vasoconstriction usually associated with a rise in systolic pressure, suppression of appetitite, stimulation of peristalsis and, with larger doses_ nausea of central origin which may be associated with vomiting.

Nicotine is rapidly metabolized by man and certain other mammals. The primary pathway through (—)-cotenine to ϑ-(3-pyridyl)-ϑ-methylamino-butyric acid is described in detail. The known metaholites have very low toxicity.

The rapidity of degradation to non-toxic metabolites, the results from chronic studies on animals, and the low mortality ratios of pipe and cigar smokers when compared with non-smokers indicate that the chronic toxicity of nicotine in quantities absorbed from smoking and other methods of tobacco use is very law and probably does not represent a significant health problem.

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