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COMMENTARY

DRUG ABSORPTION FROM THE LUNG

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The absorption of nonvolatile compounds from the lung is of interest from several viewpoints. For instance, the respiratory tract might provide a useful route of administration for systemically acting drugs that ordinarily require parenteral injection because of inadequate absorption from the intestine. On the other hand, from quite the opposite point of view, investigators are concerned about the undesired systemic effects of aerosolized drugs that are inhaled for local action within the respiratory tract, for example, bronchodilators, anti-inflammatory steroids, and certain antibiotics. In addition, problems abound concerning the systemic toxicity that results from unintentional inhalation of insecticides, herbicides, industrial chemical dusts, and numerous other airborne substances. Finally, investigators are interested in using drugs as probes to explore the permeability characteristics of the respiratory tract epithelium, not only in the healthy lung but also in the diseased organ.

Until recently, little quantitative information has been available concerning the absorption of nonvolatile substances from the lungs. In 1857, Claude Bernard reported the lethal action of curare after intratracheal administration to dogs. This observation and other early qualitative studies of pulmonary absorption have been reviewed previously [1–4]. In more recent years, although a number of drugs and other organic solutes have been reported to be absorbed from the respiratory tract of mammals, nearly all the investigations have remained qualitative in design (see Refs. 1 and 2). For example, pulmonary absorption has been demonstrated by the pharmacologic effect observed after intratracheal administration of a drug solution or inhalation of a drug aerosol. In other studies, absorption has been established by detection of a substance in blood, lymph or urine after administration into the respiratory tract. Except under special circumstances, these criteria give no idea of the rate or extent of drug absorption, because the data are dependent on such variables as the distribution, metabolism and excretion of drugs. In addition, in absorption studies with aerosols, measurements of blood or urine concentrations of drug have not permittted estimation of the extent of absorption because the dose of drug administered (amount inhaled and retained) has been unknown. Furthermore, in some studies of pulmonary absorption, precautions have not been taken to eliminate possible absorption from sites such as the oral cavity, nasal passages, skin or gastrointestinal tract.

For some time, investigators have tended to believe that drug absorption from the respiratory tract is a rapid process [5]. However, in the near absence of quantitative reports on absorption rates, one may wonder how such a notion became established. Perhaps it arose from clinical and laboratory observations of a rapid pharmacologic response to certain drugs inhaled as aerosols or smokes, or from the toxic effects readily produced on inhalation of certain aerosolized poisons.

This brief review, which deals primarily with recent quantitative studies of pulmonary absorption, will show that, although drug absorption from the lungs can indeed occur rapidly, the rates of absorption of different compounds vary widely depending on the physico-chemical properties of the compounds and on whether absorption occurs by diffusion or by carrier-mediated transport. It will also be shown that certain medicinal agents are absorbed so slowly that administration into the lungs would not be a satisfactory route of administration in therapeutics.

EXPERIMENTAL METHODS

To estimate the rate of absorption of a drug from the lung, the investigator may measure either its disappearance from the organ or its appearance in the circulation. With the latter approach, an apparent rate constant for absorption can be calculated by kinetic analysis of the plasma concentration time curve. Although an apparent rate constant for absorption can also be obtained from data on drug disappearance from the lung [6], this method is limited to the study of compounds that are not metabolized by lung tissue. Since, in the drug disappearance method, it is necessary to assay the entire respiratory tract (tissue plus contents) for unabsorbed drug, the method has the disadvantage of requiring a larger number of animals than does the plasma concentration method, in which consecutive blood samples can be obtained from a given animal over the entire time course of an experiment.

A somewhat different method has been developed for use with aerosols of radioactively labeled drugs [7]. At the end of an aerosol exposure period, the respiratory tract is excised and assayed for unabsorbed radioactivity, and the carcass and excreta are combined and assayed for absorbed radioactivity. The sum of the two values represents the dose (amount inhaled and retained), and percentage of the dose absorbed is readily calculated. Although this method applies only to drugs that are metabolically stable in the lung, metabolism after absorption would not present a problem unless the metabolites were volatile and thus eliminated in the expired air. Of course the

method would be limited to animals small enough to fit into a tissue-homogenizing device.

With any of the above methods, it is essential that the drug be inhaled or injected through a tight-fitting tracheal cannula that is kept in place during the entire absorption experiment. Otherwise drug could escape from the lungs by mucociliary clearance [8] and reach other absorption sites, such as the oral cavity or gastrointestinal tract.

Considering the factor of drug dosage, when a small volume of drug solution is rapidly injected just above the tracheal bifurcation, and the injection catheter quickly withdrawn through the tracheal cannula [6], a precise quantity of drug is deposited within the lungs. In contrast, when an aerosolized solution of drug is inhaled through a tracheal cannula over a period of time, administration of a precise dose is not so readily achieved. Some of the inhaled aerosol particles will be deposited, but others will be exhaled; the factors governing deposition include not only the characteristics of the aerosol but also a number of physiologic variables [1, 2, 8–11]. One approach to the aerosol problem is that mentioned above, in which the dose of drug is accurately measured at the end of an experiment by whole body assay of radioactivity.

Whether a drug is administered by aerosol inhalation or intratracheal injection, there is the problem of how to assess or control the distribution of drug within the lung. Absorption rates would be expected to vary at different levels of the respiratory tree owing to the variable thickness of the epithelial lining cells and possibly to other anatomic and physiologic variables at the different levels. Although many reports in the literature deal with the pulmonary deposition of aerosols, and considerable progress has been made in the technology of aerosol generation and characterization, much remains to be learned about predicting and controlling the pattern of drug deposition at various levels of the lung [1, 2, 8–12]. With the intratracheal injection technique, very little work has been done to determine the pattern of pulmonary distribution of various administered volumes [6]. However, in a recent report comparing the pulmonary distribution of particulate material administered to rodents either by intratracheal injection (0.15 ml/100 g body weight) or aerosol inhalation [12], it was shown that the aerosol produced a more uniform distribution of material with deeper penetration of particles into the respiratory zone.

The problem of uneven distribution of drug within the lung is, in a sense, avoided in experiments in which a lobe of lung is collapsed and then filled with a saline solution containing a drug [13, 14]. However, estimations of permeability coefficients or apparent membrane pore radii in a fluid-filled lung lobe may be quite different from those in a normal, ventilated organ [15–17].

Isolated, fluid-filled lung lobes, with the vasculature perfused with whole blood, plasma or a less physiological fluid, have been used to assess the permeability of the alveolar epithelium and capillary endothelium to organic compounds [18–22]. Again, one may wonder how the permeability characteristics observed with these preparations relate to those of the normal, air-filled lung.

Preparations of the isolated, ventilated lung, perfused with blood, plasma or plasma substitutes, have been used to investigate the tissue uptake of drugs from the circulation as well as the metabolism of drugs by lung tissue [23–28]. It remains to be shown how the permeability of these preparations to drugs compares with that of the normal lung *in vivo*.

QUANTITATIVE ABSORPTION STUDIES

The term quantitative absorption studies, as used in the present discussion, shall refer to those investigations from which it is possible to calculate an absorption rate. Accordingly, excluded from this discussion will be numerous reports that present accurate data on blood or urine concentrations of drugs but which do not meet the above criterion for one or more of the following reasons: (1) insufficient data were obtained; (2) the dose of drug, usually administered as an aerosol, was unknown; or (3) drug absorption from sites other than the lung (nasal mucosa, oral cavity, gastrointestinal tract, skin) was not prevented.

Studies in the rat. In a series of reports from this laboratory, the pulmonary absorption of a variety of drugs and other organic compounds has been investigated in the adult pentobarbital-anesthetized rat using the following experimental method [6]. The trachea was exposed through a ventral midline incision in the neck, and a 2.5-cm length of polyethylene tubing (PE 240), which served as a tight-fitting tracheal cannula, was inserted through an incision between the fourth and fifth tracheal rings caudal to the thyroid cartilage to a depth of 0.6 cm. With the animal resting on its back, 100 μl of a drug solution in modified Krebs–Ringer phosphate solution (pH 7.4) was injected into the lungs through PE 20 tubing. The injection tubing was inserted through the tracheal cannula to a point approximately 1 mm above the bifurcation of the trachea, the solution injected rapidly (1–2 sec), and the tubing quickly withdrawn. The incision in the skin was then closed around the sides of the tracheal cannula, anesthesia continued, and body temperature maintained at 37°. At the end of an absorption period, the lungs and trachea were excised from the animal and assayed for unabsorbed drug. A semilogarithmic plot of percentage of dose unabsorbed against time yielded a straight line from which an absorption rate constant or half-time (time for 50 per cent of a dose to be absorbed) could be calculated.

Studies with a number of lipid-insoluble substances ranging in mol. wt from 60 to 75,000 and including neutral molecules (urea, erythritol, mannitol, sucrose, ouabain, dihydroouabain, cyanocobalamin, inulin and dextran), anionic compounds (heparin, sulfanilic acid and *p*-acetylaminohippuric acid) and quaternary amines (tetraethylammonium, diquat and procaine amide ethobromide) have indicated that these compounds are absorbed from the lung by a non-saturable process of diffusion, and that the absorption rates are related to the size of the molecules—the higher the mol. wt, the slower the rate of absorption [6, 29–32]. From a semilogarithmic plot of absorption rate constant against coefficient of free diffusion (water, 37°) of these substances, a curve has been obtained that makes it possible to predict the

absorption rate of other lipid-insoluble compounds from their calculated or measured diffusion coefficient [30]. Analysis of the data in terms of the pore theory of membrane permeability suggests that the pulmonary epithelium contains at least three different populations of pore size. Each size of pore presumably allows molecules below a certain size to pass at rates related to their diffusion coefficients, while markedly restricting the passage of larger molecules [6].

The above results indicate that absorption of lipid-insoluble substances from the lungs is a very rapid process compared to absorption from the gastrointestinal tract. For example, the 1-hr absorption of mannitol and inulin from the small intestine of the rat is less than 2 per cent of the amount administered [33], whereas, with the rat lungs, the 1-hr absorption of mannitol is about 50 per cent, and that of inulin 17 per cent of the administered dose [6]. Although the marked difference between intestinal and pulmonary absorption rates would presumably be seen also for substances of higher mol. wt, the rates at which these latter substances are absorbed from the lungs can hardly be said to be rapid. For example, the absorption half-time in the rat lung is 9.2 hr for heparin and 28 hr for dextran [6, 30].

Results of absorption studies with a wide variety of lipid-soluble drugs are consistent with the idea of a lipoid-pore type of membrane for the respiratory tract epithelium. A number of antibiotics [34], sulfonamides [35], cardiac glycosides [29], bronchodilators [36], and miscellaneous weak acids and bases [31, 32, 37] appear to be absorbed from the rat lung by simple diffusion at rates roughly related to their lipid/water partition coefficients at pH 7.4; in general, the greater the coefficient, the more rapid the absorption rate. As with other body membranes [38], occasional exceptions to the relationship do occur, and the best correlations are seen among compounds of similar chemical structure [29, 34, 35]. Compounds of lowest lipid solubility show an absorption rate approaching that which would be predicted for absorption through membrane pores as described above. For a partly ionized weak acid or base, the lipid-insoluble ionized form would be absorbed predominantly by the pore route at a rate determined by its molecular size, whereas the lipid-soluble non-ionized form would be absorbed not only through the pores but also through lipoid regions of the membrane, the latter rate being determined mainly by the partition coefficient of the non-ionized form. That the lipoid route is the predominant pathway for absorption of highly lipid-soluble drugs becomes clear when one considers that some of these compounds have absorption half-times of 1 min or less [29, 31, 35] as compared to half-times of approximately 1 hr for drugs (mol. wt 150–200) absorbed by way of the pore route alone [6, 31, 32, 35]. When weak acids or bases are administered into the lungs in solutions of pH 6.2 to 8.4, the acids are absorbed most rapidly at the low pH value and the bases most rapidly at the high pH value, as would be expected for a lipoid membrane that is preferentially permeable to the non-ionized form of a compound [39].

Not all drugs are absorbed by diffusion alone. For instance, the organic anions phenol red and disodium cromoglycate are transported into the bloodstream in part by a specific carrier-type transport process and in part by diffusion [40, 41]. The carrier component of absorption is saturable and is inhibited by certain other organic anions but not by organic cations. Phenol red and disodium cromoglycate appear to share a common transport process. Interestingly, both compounds are taken up by lung slices by a process showing all the characteristics of active transport [42, 43].

In a preliminary study with aerosols of radioactively labeled drugs, in which the administered dose was estimated by whole body assay of radioactivity and extrapulmonary absorption prevented by a tracheal cannula and plastic animal coverings [7], lipid-insoluble compounds such as mannitol, sucrose and inulin were absorbed faster than when administered by intratracheal injection. The increased absorption rates with aerosols possibly reflect greater penetration into alveolar regions where the absorbing membrane is thinnest.

Studies in other species. In preliminary investigations of drug absorption from the lungs of mice [44] and rabbits [45], the intratracheal injection technique described above for the rat has been used with appropriate modifications for the size of the animals and morphometry of the lungs [46, 47]. Lipid-insoluble compounds were absorbed 2 to 3 times more rapidly in the mouse than in the rat, and 1.3 to 3 times more slowly in the rabbit than in the rat. In contrast, a lipid-soluble drug, procaine amide, was absorbed at a similar rate in all three species. The results suggest that the pulmonary membrane of the mouse is more porous, and that of the rabbit less porous, than that of the rat.

Studies in the rat with lung damage. The effect of various types of lung damage on the permeability of the lung to drugs has been investigated by the intratracheal injection technique described above. Lipid-insoluble drugs showed increased absorption rates in the presence of experimental silicosis [48], an emphysema-like condition produced by inhalation of aerosolized papain [49], lung damage produced by intratracheally injected 1% nitric acid solution [50], or lung damage resulting from oral administration of the herbicide paraquat [51]. The results suggest that all four types of damage increase the porosity of the pulmonary epithelium. Although absorption of the lipid-soluble drug procaine amide in silicotic and emphysematous rats was the same as in normal animals, this compound did show an increased absorption rate after nitric acid or paraquat damage. Thus, in the latter two conditions, there appear to be changes in the integrity of lipoid regions of the membrane as well as changes in porosity.

Studies in the neonatal rat. In preliminary drug absorption studies with newborn rats [52–55], the intratracheal injection technique described above has been modified for the size and lung morphometry [56] of the animals. Lipid-soluble drugs, such as procaine amide and sulfisoxazole, were absorbed at similar rates in animals of all ages studied (3-, 6-, 12-, 15-, 18- and 27-days-old and adults). In contrast, lipid-insoluble compounds, such as mannitol, tetraethylammonium and *p*-aminohippuric acid, were absorbed roughly two times more rapidly in younger

rats (3- to 12-days-old) than in older animals (18-day, 27-day or adults). The results suggest that the pulmonary epithelium of 3- to 12-day-old rats has a greater porosity than that of older animals [52]. Interestingly, treatment of newborn rats with thyroxine or cortisone in the first few days of life appears to accelerate development of the pulmonary epithelium, since the high porosity disappears at a much earlier age in treated animals than in controls [53, 54]. Additional preliminary studies have shown that while the high porosity of the neonatal lung is evident with most lipid-insoluble drugs—those in a mol. wt range of 122–1355—molecules considerably larger or smaller than this may be absorbed at the same rates in neonates and adults. A possible interpretation of this finding is that the pulmonary epithelium contains pores of at least three different sizes, and that only those of intermediate size are more numerous in neonatal rats than in adults [55].

CONCLUSION

From the foregoing review, it is clear that improvements and innovations in experimental methodology are needed to better investigate the permeability of the lung to nonvolatile substances. Certainly, refinements in quantitative aerosol techniques would be an important aid. Compared to intratracheal injection methods, aerosol administration would give a more uniform distribution of material throughout the organ and come closer to duplicating the conditions under which most nonvolatile substances are inhaled by man and animals. New ideas are needed on how to assess permeability at different levels of the respiratory tree. Moreover, many fundamental questions need to be answered. For example, what actually happens to a droplet of drug solution upon becoming deposited on the surface of the alveolar or bronchiolar epithelium? What is the influence of the alveolar surface coating [57, 58] on the fate of inhaled drugs? How rapidly do dry aerosols (dusts) of drugs become dissolved in the respiratory tract surface coating, and what factors determine the dissolution rate? What is the nature of membrane pores in the pulmonary epithelium, and what physiologic and pathologic factors influence the size, number and distribution of pores throughout the respiratory tract? What types of membrane carriers are present in the pulmonary membrane, and what is their distribution? What are the effects of environmental variables, physiologic variables and lung diseases on the absorption rate of inhaled substances? Do inhaled or systemically administered drugs alter the permeability characteristics of the pulmonary epithelium? These questions are only a few of the many that might be asked as we begin to probe deeper into the question of the permeability of the lung to drugs.

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