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USE OF NIACIN AS A DRUG

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INTRODUCTION

In this review we take the position that there are no essential differences between nutrients and drugs when they are viewed as substances that react with receptors in living organisms. Biology today deals with substance ⇋ receptor interactions and the consequences thereof at a molecular level (2). The actions of nutrient or drug will depend upon the affinity for specific (or nonspecific) receptors and the intrinsic activity once the substance ⇋ receptor reaction has occurred (33). Many factors enter into the final action of a drug in the intact human. These include primarily the dose, route of administration, biotransformation mechanisms, and the previous state of health or disease.

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The dose is the most important of these factors and particularly in the case of vitamins has led to the discovery of new uses as well as unexpected toxicity (31). The aura surrounding the miraculous cures of deficiency states by modest doses of vitamins has led to exploitation of the effects of large doses by manufacturers, scientists, and clinicians (41). The term meganutrients or megavitamin doses has been applied, presumably meaning extremely large (one million times the RDA). More appropriate is the concept of pharmacologic doses whereby a pharmacodynamic action is evidenced that is distinct from the nutrient function. These doses are generally in the range of 100 to 200 times the RDA and certainly not in the so-called mega range (30).

Almost every vitamin and many nutrients have been explored for pharmacologic activity, apart from their nutrient functions, when given in higher doses, by a different route of administration, or in a congener form. Thus vitamin A in the *cis*-retinoic acid form cures cystic acne; vitamin D is really a hormone that can be used to treat hypoparathyroidism and other hypocalcemic syndromes; choline is of possible benefit in certain CNS degenerative diseases; branched chain amino acids are used to treat hepatic failure. An attempt has been made to unify and define the use of nutrients as pharmacologic agents under the heading "Nutritional Pharmacology" (71). Unfortunately, no underlying theory has been established to substantiate this field. Some researchers suggest that when a chemical classified as a nutrient is used in a larger dose or by a different route of administration the chemical may act on different receptors than those that serve its more natural nutrient function. This theoretical approach has been well described as the "Occupancy Theory" (47). Simply stated, the theory says that, "A drug with a low affinity and a low intrinsic activity must be present in a large concentration to interact with enough receptors to bring about a response." An excellent example of this concept is the ability of thiamine to act as a neuromuscular blocker in cats when administered intravenously in a dose about 15–20 times the usual parenteral thiamine human dose of 100 mg (29).

One might also predict that the biotransformation of a large dose of a nutrient or drug might produce a different proportion of metabolites. In this sense, a large dose might cause a nutrient to act as a prodrug and produce a metabolite with pharmacologic activity that could not be evidenced at the nutrient dose (74).

Pellagra characterized by the classical triad of dermatitis, diarrhea, and dementia is dramatically cured by niacin or tryptophan. It is not surprising that clinicians, or even lay persons, would attempt to cure other diseases with symptoms that bear a resemblance to the symptoms of pellagra. Yet accurate knowledge of the exact role niacin and tryptophan played in nutrition did not materialize until the middle to late 1930s (59). The use of niacin as a drug was

established when the ability of nicotinic acid to significantly lower serum cholesterol in man was discovered in the early 1950s (4). Since that time niacin has been used with some success in many disease states in doses far greater than the RDA. These applications of niacin were reviewed in 1983 (81). The present review deals mainly with the literature of the past 10 years and concentrates on the antihyperlipidemic function of nicotinic acid, which has been the outstanding therapeutic use of large doses.

NIACIN AS A NUTRIENT

Niacin is a generic name that can apply to both nicotinic acid and nicotinamide. Both compounds are equally effective as nutrients or cofactors. However, their metabolism is different, and nicotinic acid has found more uses as a drug and indeed is less toxic than nicotinamide. When their nutrient function is the subject of discussion the term *niacin* will be used; when their actions as drugs are discussed, specific reference to nicotinic acid or nicotinamide will be made.

Niacin is a precursor of nicotinamide adenine dinucleotide (NAD). Condensation of nicotinic acid and phosphoribosyl pyrophosphate forms nicotinate ribonucleotide, a key intermediate on the pathway of NAD biosynthesis. Alternatively, nicotinate ribonucleotide can be formed from tryptophan, by way of quinolinic acid. Thus, tryptophan can satisfy the requirement for dietary nicotinic acid. Nutritional studies in humans have indicated that about 60 mg of tryptophan provides 1 mg of niacin equivalent. The recommended dietary daily allowance (RDA) for niacin equivalents (NE) for adults is 6.6 mg per 1000 kcal or at least 13 mg at caloric intakes of less than 2000 kcal (39, 59, 67).

In the pathway of NAD biosynthesis, nicotinate ribonucleotide subsequently acquires an adenylic acid group from ATP in a reaction catalyzed by NAD pyrophosphorylase to form desamido-NAD. Addition of an amide group from glutamine to the nicotinic acid portion of the molecule completes the synthesis of NAD. The latter can be phosphorylated at the 2 position of the ribose ring to form NADP. Both NAD and NADP can be reduced to give NADH and NADPH, respectively, in oxidation-reduction reactions.

Nicotinamide is produced from hydrolysis of excess NAD by NADase (NAD hydrolase). Nicotinic acid can be formed from nicotinamide by action of a deamidase. A key fact about the reactions involved in mammalian NAD biosynthesis is that no known enzyme can convert nicotinic acid directly to nicotinamide. The amide form of niacin (nicotinamide) arises only from degradation of NAD. Thus, although nicotinamide is the form of niacin biologically active in the coenzyme function of NAD, both nicotinic acid and

nicotinamide can function as vitamins for NAD biosynthesis. However, nicotinamide must be converted back to nicotinic acid prior to incorporation into NAD because no pathway exists for direct incorporation of nicotinamide into an NAD precursor or into NAD itself.

The nicotinamide adenine dinucleotides participate in a wide array of oxidation-reduction reactions catalyzed by dehydrogenase or oxido-reductase enzymes. Virtually every aspect of cellular metabolism involves NAD/NADH or NADP/NADPH-linked systems. In the absence of sufficient supplies of niacin precursors for NAD biosynthesis, cellular functions and life itself would be impaired. Thus, niacin (or tryptophan) is a critical nutrient for humans (39).

The lack of direct conversion of nicotinic acid to nicotinamide is relevant for understanding the nonequivalent pharmacologic effects of these compounds. As discussed below, pharmacologic doses of nicotinic acid and nicotinamide are biotransformed to different major metabolites.

NIACIN AS A DRUG

Few of the pharmacologic actions of nicotinic acid are shared by nicotinamide. The obvious pharmacologic effect of an acute administration of a large dose (1 g or more) of nicotinic acid is vascular (the flush). Lowering of serum cholesterol, of much greater clinical interest, occurs only after weeks of therapy with large (2–6 g) daily doses; this suggests a metabolic mechanism for the anti-hyperlipidemic effect. Nicotinamide shares none of these actions.

Biotransformation Patterns

One clear distinction between nicotinic acid and nicotinamide is the manner by which these two compounds are biotransformed, or metabolized, in the body after administration at pharmacologic doses. Nicotinic acid is biotransformed mainly by conjugation with glycine into nicotinuric acid, whereas nicotinamide is biotransformed primarily to *N*-methylnicotinamide and oxidized pyridone carboxyamide derivatives. In the rat, administration of a pharmacologic dose of nicotinic acid (500 mg/kg) resulted in urinary excretion of 55% of the dose as unchanged nicotinic acid and 15% as nicotinuric acid during the first 24 h (70). At a dose of 100 mg nicotinic acid/kg, over 50% of the dose was recovered as nicotinuric acid (60). By contrast, administration of nicotinamide at 500 mg/kg resulted in urinary excretion of 51% of the dose as unchanged nicotinamide, 17% as *N*-methylnicotinamide, 16% as nicotinuric acid, 8% as nicotinic acid, and 8% as 2− and 4-pyridone carboxyamide metabolites (70). At a lower dose of 100 mg nicotinamide per kilogram, relatively higher amounts of metabolites were recovered in the urine as

N-methylnicotinamide and as pyridones (60). Niacin metabolites are excreted exclusively in the urine.

Studies of the pharmacokinetics of nicotinic acid in human volunteers have demonstrated the importance of glycine conjugation in elimination of the drug. Concomitant administration of aspirin (salicylic acid), which is also biotransformed by glycine conjugation, slowed the elimination of nicotinic acid from the plasma (26). After aspirin administration, a substantial decline in plasma nicotinuric acid concentrations occurred and was accompanied by a rise in steady-state nicotinic acid concentrations. The study is particularly relevant because aspirin is effective in counteracting the flush observed as a side effect of high-dose nicotinic acid therapy. Coadministration of aspirin and nicotinic acid appears to increase the bioavailability of nicotinic acid by promoting higher and sustained plasma levels of nicotinic acid (26).

The existence of distinct biotransformation patterns for these two forms of niacin may, in part, explain why these two compounds do not share the same spectrum of pharmacologic activities. Nicotinic acid and nicotinamide are clearly handled differently by endogenous enzyme systems involved in drug metabolism and elimination. Thus, the fact that these compounds exhibit differing pharmacologic activities is not surprising. The findings suggest that nicotinic acid and nicotinamide interact with different receptors or target enzymes, when used in larger doses, and perhaps via different metabolites.

Pharmacologic Actions of Nicotinic Acid

ANTIHYPERLIPIDEMIC The beneficial effects of nicotinic acid in treatment of hyperlipidemia are consequences of at least four interrelated effects on lipid and lipoprotein metabolism. These include (*i*) inhibition of lipolysis in adipose tissue, (*ii*) inhibition of the synthesis and secretion of VLDL by the liver, (*iii*) a lowering of serum levels of lipoprotein(a), a variant form of LDL, and (*iv*) an increase in serum levels of HDL accompanied by a shift in HDL subtype distribution. As discussed in this section, the molecular and cellular mechanisms responsible for these effects have been elucidated only in part.

Inhibition of lipolysis in adipose tissue Pharmacologic doses of nicotinic acid decrease mobilization of fatty acids from adipose tissue by inhibiting the breakdown of triglycerides through lipolysis (19). Adipose tissue lipolysis is regulated by hormones and paraendocrine agents through the c-AMP system. Elevated levels of c-AMP activate a protein kinase that phosphorylates a hormone-sensitive lipase, thus activating the lipase to catalyze triglyceride hydrolysis. Hormonal signals are transduced through the guanine nucleotide-linked G-protein system, which interacts with adenyl cyclase to modulate cellular c-AMP levels. Both stimulatory (G_s) and inhibitory (G_i) pathways

have been identified. In fat cells, G-proteins function as transducing elements for receptors that are either stimulatory (R_s) or inhibitory (R_i). Lipolytic agents such as catecholamines, adrenocorticotropic hormone, and glucagon bind to distinct R_s receptors. The ligand-receptor complexes then interact with a common G_s protein, leading to stimulation of adenyl cyclase activity, which results ultimately in fat breakdown. Antilipolytic agents such as adenosine, prostaglandin E_2, and nicotinic acid bind to R_i receptors, which in turn interact with the G_i protein. These interactions lead to inhibition of adenyl cyclase and subsequent decreased mobilization of fat from adipose tissue (54).

Early studies showed that nicotinic acid inhibited adenylate cyclase activity in isolated hamster adipocytes, which led to a decrease in intracellular c-AMP levels (1). This inhibitory activity required the presence of both GTP and sodium ions. The concentration of nicotinic acid needed for half-maximal inhibition of adenyl cyclase was 0.6 μM; full inhibition was achieved at 10 μM. Nicotinic acid derivatives, including nicotinamide, had no effect on adenyl cyclase (1). Recent studies with isolated human adipocytes from both adults and infants have confirmed the inhibitory potency of nicotinic acid toward lipolysis; maximal inhibition was observed at a concentration of about 1 μM (58). These studies infer that nicotinic acid binds to distinct R_i receptors on the plasma membrane of adipocytes, although the molecular properties of such receptors have not been characterized (54, 58).

In view of current knowledge about the functioning of G-protein systems, a likely molecular mechanism of action can be proposed for the antilipolytic effect of nicotinic acid (7, 20). Namely, nicotinic acid binds to a specific R_i receptor on the plasma membrane of adipocytes. The occupied receptor, in turn, forms a complex with the inhibitory G_i-protein. In the presence of GTP, the G_i-protein dissociates into alpha and beta-gamma subunit moieties, respectively, as well as dissociates from the receptor. Subsequently, the newly activated G_i-protein inhibits adenyl cyclase, which leads to a decrease in c-AMP levels. Alternatively, the released beta-gamma subunit complex binds an alpha subunit of the G_s type, resulting in deactivation of the competing stimulatory pathway and a subsequent decrease in cellular c-AMP. Decreased c-AMP will then lead to lessened activity of the lipase and thus diminished breakdown of depot fat.

Alternative mechanisms may, however, also be involved in the antilipolytic action of nicotinic acid. This possibility was suggested by the observation that nicotinic acid inhibited forskolin-induced c-AMP production in rat adipocytes and other cells (55). Forskolin is a diterpene compound that activates adenyl cyclase by a receptor-independent mechanism. Adipocytes from both fed and fasted rats showed similar titration curves for inhibition of forskolin-stimulated c-AMP synthesis by nicotinic acid. These results indicate that

nicotinic acid can inhibit receptor-independent c-AMP formation. Nicotinic acid may interact with adenyl cyclase directly, rather than indirectly through a G-protein coupled receptor. Measurements of nicotinic acid binding to adipocyte plasma membrane fractions and characterization of the hypothesized protein receptor are needed to clarify the mode of action of nicotinic acid on lipolysis.

Inhibition of VLDL synthesis by the liver Many studies have established that nicotinic acid treatment decreases serum levels of both triglycerides and cholesterol. These lipid changes are found mainly in the VLDL and LDL fractions. Studies of the turnover of lipoproteins in hyperlipidemic patients have shown that the rate of synthesis of VLDL is decreased by nicotinic acid treatment (34). The predominant effect is a reduction in hepatic triglyceride synthesis, thereby limiting overall assembly and secretion of VLDL from the liver.

The antilipolytic effect of nicotinic acid in adipose tissue is thought to be responsible, at least in part, for the inhibition of VLDL synthesis in the liver. Fatty acids mobilized from adipose tissue are normally used for lipoprotein synthesis by the liver, especially during periods of fasting. Thus, decreased availability of free fatty acids in the blood during nicotinic acid treatment will reduce the ability of the liver to synthesize triglycerides for subsequent assembly into lipoproteins. Since LDL are derived mainly from VLDL as a result of normal lipoprotein catabolic processes, a decrease in VLDL synthesis and secretion by the liver will eventually cause a decline in circulating levels of LDL. However, diurnal variations in the extent of inhibition of lipolysis by nicotinic acid have suggested that this is not the sole mechanism by which hepatic VLDL synthesis is reduced (49). Additional direct effects of nicotinic acid on the liver likely contribute to the lowering of serum VLDL and LDL levels.

The mechanisms responsible for the control of serum cholesterol levels are now reasonably well established (13). Two major pathways—de novo synthesis from endogenous precursors and reuptake of circulating cholesterol via LDL receptors—combine to modulate serum cholesterol levels. Both of these pathways are subject to feedback regulation. Thus, high hepatic cholesterol levels repress the synthesis and activity of 3-hydroxy-3-methylglutaryl (HMG) CoA reductase, the enzyme that catalyzes the rate-determining step in cholesterol biosynthesis. Endogenous cholesterol likewise represses the synthesis of LDL receptors, which leads to decreased uptake of additional cholesterol from the circulation. The fact that nicotinic acid lowers total serum cholesterol substantially suggests that at least part of its mechanism of action may involve effects on recognized key aspects of the cholesterol-regulating system (34, 43).

A number of studies in animals as well as in hyperlipidemic patients have indicated that nicotinic acid inhibits endogenous synthesis of cholesterol (43). In humans, incorporation of radioactive acetate into mevalonic acid was decreased during nicotinic acid therapy, suggesting an inhibition of cholesterol biosynthesis at the level of HMG CoA reductase (53). Plasma levels of squalene, a later intermediate on the pathway of cholesterol biosynthesis, were also decreased (53). Thus, at least part of the antihyperlipidemic action of nicotinic acid appears to arise from inhibition of endogenous cholesterol biosynthesis. The effect of nicotinic acid treatment on LDL receptor activity has not, to our knowledge, been studied directly, presumably because the general consensus is that nicotinic acid affects synthesis rather than catabolism of lipoproteins.

Apolipoprotein B-100 (apo B) is the major protein component of VLDL. In monkeys, the incorporation of labeled amino acids into the protein fraction of VLDL was decreased after nicotinic acid treatment (57). Likewise, isotope studies in humans showed that turnover of the protein moiety of LDL was decreased, without any change in the fractional catabolic rate for LDL, after nicotinic acid treatment (45, 79). These results support an inhibition of the synthesis of apolipoprotein-B during nicotinic acid treatment. The mechanism by which this inhibition is accomplished has not been studied.

Lowering of lipoprotein(a) Recent clinical studies have indicated that nicotinic acid therapy decreased serum levels of lipoprotein(a) (16). Lipoprotein(a), Lp(a), is a variant form of LDL that contains apolipoprotein B (apo B), the normal constituent of VLDL, and apo (a). Apo (a) shows structural homology with plasminogen and is bonded to apo (B) by disulfide linkages in Lp(a). Nicotinic acid at a dose of 4 g per day administered to hyperlipidemic patients for 6 weeks decreased serum Lp(a) levels an average of 38% (16). There was a linear relationship between the percent decrease of Lp(a) and the diminution in LDL cholesterol levels. The authors suggested that nicotinic acid may act by inhibiting the synthesis of apo (B), since this is the common component of both Lp(a) and LDL (16).

Elevated plasma levels of Lp(a) are considered to be an independent risk factor for the development of cardiovascular disease (6, 11). Lp(a) is regarded as a particularly atherogenic lipoprotein and has been identified in atherosclerotic lesions by immunocytochemical techniques (36). Lp(a) may also play a key role in thrombosis because of its structural similarity to plasminogen (61). Lp(a) competes with plasminogen for binding to surface receptors on endothelial cells, thereby impeding activation of plasminogen to plasmin (36, 61). The consequence of such an action would be inhibition of thrombolysis and thus a favoring of thrombosis (61).

The ability of nicotinic acid therapy to decrease serum levels of Lp(a) is

distinctive among antihyperlipidemic drugs. Only neomycin shares this ability, particularly when used together with nicotinic acid (35). By contrast, a study with the new HMG CoA reductase inhibitors lovastatin and simvastatin observed an average 33% elevation of serum Lp(a) levels coincident with an average 45% lowering of VLDL and LDL cholesterol levels in hyperlipidemic patients (50). These results suggest significant differences in the metabolism of Lp(a) and LDL. The HMG CoA reductase inhibitors cause an increase in the number of LDL receptors on hepatocytes as a compensatory response to the decrease in endogenous cholesterol synthesis. Increased uptake of circulating LDL via these hepatocyte LDL receptors is thought to be the major mechanism for reduction of serum cholesterol in response to HMG CoA reductase inhibitor therapy. Additionally, in vitro studies have indicated that Lp(a) is a poor substrate for LDL receptors (50, 52). The differences between the effects of nicotinic acid and the HMG CoA reductase inhibitors on Lp(a) metabolism point toward differences in the mechanisms of action of these drugs at the molecular and cellular levels. Drugs that decrease lipoprotein synthesis, as opposed to increasing lipoprotein catabolism, may possibly reduce Lp(a) levels (50). As noted earlier, this effect might arise from nicotinic acid inhibition of apo (B) synthesis in the liver.

Increase in HDL Nicotinic acid therapy lowers serum levels of VLDL and LDL, as well as total cholesterol and triglycerides, but increases HDL and HDL-associated cholesterol (3). Nicotinic acid also alters the relative distribution of HDL between subtypes defined operationally by differing densities during ultracentrifugation. These subtypes are HDL2 (d = 1.063–1.125 g/ml) and HDL3 (d = 1.125–1.210 g/ml), respectively. The larger, less dense HDL2 are thought to be formed from precursor HDL3 by acquisition of surface components such as free cholesterol from chylomicrons and VLDL undergoing lipolysis (8, 51). HDL2 is regarded as a beneficial form of the lipoprotein that is possibly active in removal of cholesterol from atherosclerotic lesions. Nicotinic acid therapy is commonly associated with an increase in the HDL2:HDL3 ratio. In a study with healthy volunteers, administration of 1 g nicotinic acid 3 times per day for 3 weeks decreased plasma total cholesterol levels an average of 15% (69). The decrease was seen in the VLDL and LDL fractions, while HDL cholesterol increased 23%. The ratio of HDL2:HDL3 was increased more than 3-fold after nicotinic acid treatment (69).

Previous studies have reported that the effects of nicotinic acid on HDL depend on the specific clinical type of hyperlipidemia (18, 66). By contrast, a recent study found that patterns of HDL changes were similar in types IIa, IIb, and IV hyperlipidemic patients (80). The increase in total HDL cholesterol

was accounted for entirely by an increase in the HDL2 fraction (80). Temporal differences have been noted in the effects of nicotinic acid on the different lipoprotein classes. In Type IV hyperlipidemic patients treated with nicotinic acid, the rise in HDL levels occurred well after the decline in VLDL had stabilized (18). This dissociation in time of changes in the amounts of various lipoproteins suggests that different biochemical mechanisms are responsible for the effects of nicotinic acid treatment on VLDL and HDL.

Elevated HDL may be due, in part, to a decrease in the rate of catabolism of associated apolipoproteins. In Type IV hyperlipidemic patients the half-life for plasma apolipoprotein A-I was increased about 20% after nicotinic acid therapy, whercas that of apo A-II was unchangcd (66). In the same patients, apoprotein biosynthesis rates were unaffected by nicotinic acid (66). In agreement with these observations, an increase in the absolute amount of apo A-I but no change in the amount of apo A-II were seen after nicotinic acid therapy in another study (49). Apo A-I is an activator for lecithin cholesterol acyl transferase (LCAT). This enzyme plays a major role in removal of cholesterol from peripheral tissues through the process of reverse cholesterol transport. In addition, HDL3 is a primary substrate for LCAT. HDL3 picks up unesterified cholesterol from peripheral tissues and by doing so is converted to HDL2 upon action of LCAT (38, 51). Thus, part of the antihyperlipidemic effect of nicotinic acid may arise from inhibition of apo A-I degradation, which, in turn, facilitates LCAT activity and mobilization of cholesterol for subsequent removal through the hepatic LDL receptor system. This mechanism might also account for the shift toward HDL2 subtype after nicotinic acid administration. Further studies are needed to elucidate the molecular and cellular mechanisms responsible for inhibition of apo A-I catabolism by nicotinic acid.

VASODILATION The vasodilation of nicotinic acid may be induced by as little as one milligram intravenously but is much more intense at higher doses. It involves mainly the face and upper trunk. Grossly it resembles the "menopausal flush" experienced by women in menopause. It is accompanied by an unpleasant sensation of warmth and often pruritis and sometimes develops into a skin rash. It occurs immediately upon injection of the nicotinic acid. The visible skin flush lasts only about 1 or 2 min, but vasodilation can be measured even in the lower limbs for some 30 min thereafter (81). It is not antagonized by histamine or adrenergic blockers. Partial antagonists are prostaglandin synthesis inhibitors such as indomethacin, aspirin, and other salicylates (72). Prostaglandin E_1 and nicotinic acid both cause a rise of skin temperature in the guinea pig ear model. Both also raised the cAMP levels of the ear tissue. These actions could be blocked by indomethacin in the case of

nicotinic acid but not of prostaglandin (5). These effects are the basis for the clinical use of aspirin 30 mins before each dose of nicotinic acid to block the flush reaction and thereby give partial relief to most patients. The vasodilation action of nicotinic acid is not understood. The flush reaction disappears after weeks of continued daily nicotinic acid therapy, and this tolerance development is not explained. Recent discoveries attribute the transduction mechanism of vascular smooth muscle relaxation to the production of nitric oxide (62). This mechanism is true for endothelial relaxing factor and nitrates and one wonders if nicotinic acid may also affect this mechanism.

FIBRINOLYSIS Parenteral doses of nicotinic acid cause a significant fibrinolytic effect; oral nicotinic acid, no matter how large the dose, does not (81). The fibrinolytic effect only occurs with the first bolus dose. Subsequent doses or continuous intravenous infusion are inactive. This effect severely limits clinical use (24). With the advent of clinically effective fibinolytic agents such as tissue plasminogen activator (alteplase), streptokinase, and urokinase, interest in the fibrinolytic activity of nicotinic acid remains only as a curiosity (28).

Pharmacologic Actions of Nicotinamide

Nicotinamide is an inhibitor of poly(ADP-ribose) synthetase in pancreatic B-cells. Pretreatment of rats with nicotinamide prevented induction of diabetes by alloxan or streptozotocin (76). These experimental diabetogenic agents cause DNA strand breaks in β-cells. This process causes stimulation of poly(ADP-ribose) synthetase, an enzyme involved in DNA repair, thereby depleting intracellular NAD. In addition, daily administration of 0.5 g/kg nicotinamide to partially depancreatized rats improved glucose tolerance and decreased urinary glucose excretion substantially (82). In human type I insulin-dependent diabetes, nicotinamide administration extended the length of the insulin-free remission phase following initial control of the disease with insulin therapy. The authors suggested that nicotinamide may slow the destruction of β-cells or preserve residual β-cell function (77), presumably by elevating NAD levels. Additional studies are needed to clarify the mechanism of action of nicotinamide on pancreatic β-cells and the possible utility of nicotinamide in the treatment of diabetes.

A similar role for nicotinamide has been discussed in regard to carcinogenesis (14). Many carcinogens cause strand breaks in DNA. Strand breaks stimulate nuclear poly(ADP)-ribosylation as a repair process; this process depletes cellular NAD, because NAD is the substrate for the ADP-ribosylation reaction. Thus, by augmenting cellular NAD levels or by inhibit-

ing the poly(ADP-ribose) synthetase, nicotinamide or nicotinic acid might modulate the outcome of a DNA-damaging event. Whether such an action would prevent or enhance the development of cancer is not clear, however. No studies have specifically linked niacin deficiencies or excesses with in vivo carcinogenesis in either animals or humans (14). Further studies are needed to resolve the role, if any, of niacin in carcinogenesis.

Structure-Activity Relationships

ANTAGONISTS No analogues of niacin have been found that are superior to the natural substance for the nutrient function. Many niacin antivitamins exist, but pyridine-3-sulfonic acid, 3-acetylpyridine and 6-aminonicotinamide have been most studied (32). No important clues to the pharmacological actions of nicotinic acid have emerged from the study of antivitamin analogues. However, the niacin antivitamins have important potential as drugs. The analogue 6-aminonicotinamide has been tested clinically as an anticancer drug but proved to be too toxic (42). On the other hand, topically applied 6-aminonicotinamide has beneficial effects in psoriasis provided that systemic niacin is co-administered to counteract generalized toxicity (83). The antituberculosis drug isonicotinic acid hydrazide, isoniazid (INH), can precipitate pellagra (25). In general the niacin antivitamins have been extensively explored for antibacterial activity (81). Niacin itself can be inhibitory to several species of microorganisms (10, 81). The herbicide Paraquat, 2,2'-dimethyl-4,4'-bipyridinium dichloride, can be considered, in part, a niacin antagonist. Its high toxicity in rats can be reduced by niacin (12). Although the niacin antivitamins do not clarify the vascular and antilipidemic actions of large doses of nicotinic acid, they do open up other drug uses. These include anticancer, antibacterial, and antitoxicity uses of niacin itself.

AGONISTS A few developed drugs have attempted to exploit the pharmacological effects of niacin. Nicorandil, *N*-(2-hydroxyethyl) nicotinamide nitrate (ester), is used in Europe as a coronary vasodilator (68). However, its vascular actions may reside mainly in the organic nitrate structure rather than in the substituted pyridine moiety. Nicotinic acid benzyl ester has been used in England as a rubefacient (75). Nicotinyl alcohol (3-pyridinemethanol), Roniacol,® is marketed in Europe as a peripheral vasodilator (75). It also has some antilipidemic action, but there have been few clinical studies (56). Pentaerythritol tetranicotinate (Niceritrol®) is used as an antilipidemic in Scandinavia. It appears to be a prodrug for nicotinic acid, as its pharmacologic and clinical effects are identical (37). Another probable prodrug is inositol nicotinate (Hexopal®), which has been developed as a vasodilator for peripheral vascular disease (48).

Pharmacokinetics

Nicotinic acid is easily absorbed in the gastrointestinal tract. After an oral dose of nicotinic acid, the blood level rises from 1 to 3 μg/ml to a peak of 130 to 150 μg/ml in 4–5 h. Thereafter, the level falls rapidly and returns to control levels in about 24 h (81).

The results of pharmacokinetics studies vary depending on the method of analysis, microbiological versus biochemical. First pass effects may produce considerable quantities of niacin-like metabolites. The formulation of nicotinic acid tablets has a great effect on the rate of absorption and duration of action. In general, slow release preparations have a considerably lower peak but more sustained blood level. Curiously, sustained release nicotinic acid preparations have recently been shown to cause a higher frequency of severe hepatic failure (21, 64). Indeed, rechallenge with crystaline nicotonic acid after the sustained formulation had caused hepatitis did not produce recurring hepatocellular damage (40). This phenomenon may provide important clues to the mode of action of nicotinic acid (49). Why should a lower but more sustained blood level lead to less symptoms of flushing but more gastrointestinal symptoms? The sustained release form at equivalent or lower doses than crystalline nicotinic acid causes a higher alkaline phosphatase and a higher glutamic-oxaloacetic acid transaminase (49). This reaction suggests that nicotinic acid at high blood levels inhibits it own liver biotransformation or that the involved liver enzyme systems are less saturated at lower but sustained blood levels. Further studies of the ratio of metabolites formed at various blood levels of nicotinic acid are indicated.

The pKa of nicotinic acid is 4.85 and it is water soluble. Protein binding in the plasma is 15–30%. These facts predict a wide distribution in the water compartments of the body. However, studies with radiolabeled drug show that the rapid disappearance of nicotinic acid is due to its rapid entry into adipose tissue (17). The half-life of a one gram oral dose of nicotinic acid in humans is only 45 min (81).

The biotransformation of nicotinic acid has already been discussed and the differences between nicotinamide and nicotinic acid pointed out. Large doses of nicotinic acid are excreted in the urine mainly as nicotinuric acid. The fraction that is excreted unchanged rises with increasing doses, which indicates saturation of an enzyme system. Conversion to nicotinamide occurs, but the resulting metabolites constitute only a small excretion fraction of even a large dose of nicotinic acid (81). The shorter half-life of nicotinic acid, compared to that of nicotinamide, may be due to the more effective conversion of the latter to NAD (81).

The half-life of nicotinic acid was 42 min, but after coadministration of

indomethacin the half-life was 29 min (72). This disposition effect must be taken into consideration in studies of the relationship of prostaglandin synthesis inhibition and the flush reaction of nicotinic acid.

Toxicity

The acute toxicity of 2–6 g nicotinic acid daily may include gastrointestinal distress and mild elevations of liver enzymes besides the already described flush. After several weeks of use these symptoms may disappear completely. However, some patients go on to develop skin rashes and keratosis nigricans. In addition, long-term use may lead to jaundice, activation of peptic ulcer, vomiting, abdominal pain, and diarrhea. The hepatotoxicity including cholestatic jaundice may occur with as little as 750 mg daily and requires cessation of drug therapy (31). In the Coronary Drug Project a greater incidence of atrial fibrillation and other arrhythmias was noted in the nicotinic acid group than in the placebo control group (22). The fact that slow release nicotinic acid preparations are much more toxic to the liver than the plain formulation is of great interest and practical importance (40, 49, 64). Slow release formulations of nicotinic acid are sold in health food stores, and patients prescribed this drug can purchase any amount over the counter. Obviously slow release nicotinic acid should not be used, especially in long-term therapy.

Miscellaneous Uses

Megavitamin therapy is still popular as a faddish cure for mental disease. However, the medical use of niacin for schizophrenia has virtually disappeared not only because of the development of effective antipsychotic drugs but also because no disturbance of niacin metabolism could be found (63). Except for those with a niacin deficiency, no substantial clinical evidence of benefit from niacin therapy has been found in careful studies (46). Synthetic analogues developed in Europe as vasodilators for vascular disease have not been successful in this country (23, 37, 48, 68). Most are actually prodrugs for nicotinic acid and do not exceed its effectiveness as a vasodilator, which is at best rather weak. In any event, vasodilator therapy for peripheral vascular disease is not as popular today as in the past (65).

SUMMARY AND PROSPECTS FOR FUTURE STUDIES

The major action of nicotinic acid appears to be a reduction in the synthesis of VLDL by the liver. This action likely arises both from decreased availability of fatty acid precursors, owing to the antilipolytic effect on adipose tissue, and specific inhibition of the synthesis of apo (B). Partial inhibition of

cholesterol synthesis at HMG CoA reductase may also contribute to the decline in VLDL production. Decreased catabolism of apo A-I appears to account for the elevation of HDL and altered HDL subtype distribution. However, the molecular events responsible for these diverse actions of nicotinic acid in the hepatocyte remain to be determined.

The realization that nicotinic acid has specific receptors on adipocytes and the success of the G-protein concept in explaining the antilipolytic action of this drug is a significant advance in niacin pharmacology. It seems likely that specific receptors for nicotinic acid may also be present on hepatocytes. Such receptors might interact with the hepatocyte G-protein system in a fashion similar to that characterized for adipocytes. Alternatively, nicotinic acid plasma membrane receptors may activate other signal transduction pathways in the hepatocyte such as calcium mobilization or phosphoinositide hydrolysis. Perhaps nicotinic acid receptor-ligand complexes modulate the expression of genes, such as for apo (B), in a manner similar to steroid hormone receptors. Clearly, many interesting cell and molecular biology problems remain to be investigated in the course of understanding the mechanism of action of nicotinic acid as an antihyperlipidemic drug.

It is now appropriate to compare the antilipidemic action of nicotinic acid to that of other drugs. Nicotinic acid decreases the serum levels of both triglycerides and total cholesterol. It lowers serum levels of VLDL and LDL lipoproteins and raises the serum level of HDL. In particular, nicotinic acid raises the HDL2 fraction, which is considered to be beneficial in reverse cholesterol transport (69). This favorable pattern is shared by the HMG-CoA reductase inhibitor lovastatin, which has the advantage of a more effective cholesterol lowering effect: 20–35% compared to 10–15% for nicotinic acid (27, 44). Both agents can be used with bile acid sequestrants, cholestyramine, and colestipol to about double the cholesterol-lowering effect (73).

Nicotinic acid has had the longest period of successful use as an antihyperlipidemic and was the only drug that demonstrated a decrease in mortality in the Coronary Drug Trial after a 15-year follow-up (15, 22). Thus, nicotinic acid still holds a first-line position in the treatment of the most common types of hyperlipidemia. Nicotinic acid is especially useful in patients with severe hypertriglyceridemia (type-V hyperlipoproteinemia). It remains to be seen if lovastatin with its smaller once-a-day dosage and less side actions will replace nicotinic acid; lovastatin has been in use for only about six years (73).

The use of nicotinic acid as a vasodilator has been largely replaced by other therapy. Certainly there are enough analogues for this purpose, and further exploration would not appear to be fruitful. Other applications of nicotinic acid appear each year. None have proven of value although further explorations should not be discouraged.

Nicotinamide has few uses as a drug. Its antidiabetic action prolongs the remission that follows the onset of type I (insulin-dependent) diabetes (77, 78). Immunosuppressive therapy with cyclosporine is currently used for this purpose (9). This activity of nicotinamide should certainly be further explored even though transplantation of beta cells now appears more feasible.

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