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Gut Reactions of Radioactive Nitrite After Intratracheal Administration in Mice

Abstract. *Intratracheal administration to mice of radioactive nitrite labeled with nitrogen-13 ($^{13}NO_2^-$) (half-life, 9.96 minutes) in dosages that do not cause pharmacological perturbation reveals that oxidative and reductive reactions occur in different organs. Oxidation of $^{13}NO_2^-$ to radioactive nitrate ($^{13}NO_3^-$) predominates in the blood and liver. Reduction of $^{13}NO_2^-$ occurs in those mice that harbor intestinal microflora; this reduction does not occur in germ-free mice. The intestinal reduction products include ammonium, glutamate, glutamine, and urea. With a detection limit of about 0.01 percent of the instilled nitrogen-13, no labeled nitrosamines were detected within 30 minutes. Reduced nitrogen-13 is transported out of the intestine into the circulatory system and appears in the urine along with $^{13}NO_3^-$. The biological half-period for $^{13}NO_2^-$ destruction is about 7 minutes, and both oxidation and reduction products are formed.*

The presence of nitrogen dioxide (NO_2) and various nitrate (NO_3^-) compounds in indoor and outdoor air is well established (*1*). These chemical species are either known or suspected to form nitrite (NO_2^-) in vivo (*2*). Nitrite is known to form carcinogenic *N*-nitroso compounds in vivo by reaction with amines in the stomachs of experimental animals (*3*) and in vitro under the mediating influence of intestinal microflora (*4*). The formation of nitrosamines has been reported in rodents that were first gavaged with a precursor amine and then allowed to inhale NO_2 (*5*). Nitrous acid was postulated as an intermediate, although the mechanism or site of nitrosation was not determined. Pathogenesis attributed to NO_2^- alone has been reported, but this conclusion is still a source of debate (*6*).

Evaluation of the potential health hazard of inhaled or ingested NO_2, NO_2^-, or NO_3^- at concentrations likely to be encountered under realistic conditions has been complicated by Tannenbaum's discovery of NO_3^- synthesis in humans. This was originally attributed to the formation of NO_3^- by intestinal microflora (*7*), but more recent studies have revealed this to be a mammalian process (*8*). Saul *et al.* found that human fecal material destroys both NO_2^- and NO_3^- in vitro but did not identify any reaction product (*9*). Witter *et al.* reported that the presence of intestinal microflora decreased urinary NO_3^- excretion in rats; the speculation was offered that NO_2^- was a metabolite (*10*).

Parks *et al.* reported that radioactive ^{13}N (half-life, 9.96 minutes) as $^{13}NO_2^-$ or $^{13}NO_3^-$ (carrier dosage less than 100 ng per kilogram of body weight) was cleared from the lungs of mice to the blood and distributed into the gastrointestinal tract and other organs within 30 minutes (*11*). At this low concentration of added NO_2^- (2 to 3 n*M* in body fluids), $^{13}NO_2^-$ was 70 percent oxidized to $^{13}NO_3^-$ in blood within 10 minutes. Consequently, NO_2^- derived from nitrogenous air pollutants is partially converted to NO_3^- before reaching the gastrointestinal tract. However, mammals synthesize NO_3^- (*8*, *10*), and their oral (*12*), and possibly intestinal (*9*, *13*), microflora reduce it to NO_2^-. This presented an enigma with respect to the evaluation of health risk from either inhaled or ingested oxidized nitrogen compounds. The uncertainties regarding the metabolism of oxidized nitrogen compounds have persisted in part because analysis of trace NO_2^-, NO_3^-, or their metabolites in biological samples is difficult. Mass-spectrometric detection of stable ^{15}N allows tracer chemistry but requires dosages of ^{15}N compounds that may perturb normal biochemical processes. We have now determined that the sites of the most rapid metabolism of $^{13}NO_2^-$ in mice are the blood and the intestines. We report here the primary chemical fate in the gut and other tissues of intratracheally instilled $^{13}NO_2^-$.

In our metabolic studies, we used $^{13}NO_2^-$ to minimize any pharmacological action of the tracer (*11*). Labeled NO_2^- was prepared by the reduction of cyclotron-produced $^{13}NO_3^-$ (*14*) and concentrated into saline solution prior to instillation (*15*). All the experiments were done under "no carrier added" conditions, with specific activities of 1 to 7 Ci per micromole of NO_2^-. Consequently, total NO_2^- dosages ranged between 10 and 100 ng kg^{-1}. We determined the composition of the labeled components by using high-pressure liquid chromatography (HPLC) together with thin-layer electrophoresis (*16*).

Conventional (CV) BALB/c mice were given commercial feed and water without restriction. We assessed the effect of the microflora on NO_2^- metabolism by comparing CV mice with germ-free (GF) mice and specific pathogen–free (SPF) mice (*17*). Further comparisons were made on exenterated (small and large intestines removed) or penicillin-treated CV mice (*18*).

Table 1 shows the distribution of intratracheally administered $^{13}NO_2^-$ in the various mouse tissues and indicates the relative amounts of radioactivity in the NO_3^-, NO_2^-, and nonanionic (NA) fractions. The chemical determinations were done by anion-exchange chromatography (*16*). The NA components include all nitrogenous compounds not retained on the anion-exchange column. We determined the mean values and asymmetric error intervals about the means, using the logit transformation. This technique adequately estimates the central tendency of fractional values that are bounded by fixed margins (for example, 0 and 1) (*19*).

The fractions of whole body activity (WBA) in the various tissues of CV mice (Table 1) are consistent with a uniform distribution of ^{13}N on the basis of weight (*11*). These values show that 10 to 20 percent of the ^{13}N introduced into the lungs as NO_2^- is transported to the gut. The chemical distribution of radioactivity in the intestines of CV mice is dramatically different from that in the blood, acidic stomach contents, and other body fluids. This difference indicates that oxidation of $^{13}NO_2^-$ to $^{13}NO_3^-$ in blood is

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primarily responsible for the products observed in nonintestinal fluids and tissues. Table 1 also shows that the chemical distribution of ^{13}N in tissues of the SPF controls for GF mice is minimally different from that in CV mice.

The data for GF mice show that (i) the intestinal microflora are solely responsible for the production of ^{13}N-NA, (ii) NO_3^- and NO_2^- in the blood move into the intestine, and (iii) in the examined tissues, oxidation of $^{13}NO_2^-$ to $^{13}NO_3^-$ occurs most rapidly in the liver and blood and least rapidly in the intestine. Additional evidence for the first observation was obtained from two exenterated CV mice and one mouse treated with penicillin for 24 hours prior to the administration of $^{13}NO_2^-$ (Table 1).

Because the intestinal microflora are responsible for ^{13}N-NA production, we determined the identities of these labeled components in intestinal tissues from CV mice. The NA was separated into neutral and cationic components by cation-exchange chromatography with anion stripping to remove $^{13}NO_3^-$ and $^{13}NO_2^-$ and further characterized by thin-layer electrophoresis (*16*). Eight CV mice intratracheally instilled with $^{13}NO_2^-$ were killed as described in (*11*) except that their intestines were extracted with 100 percent methanol to stop bacterial metabolism prior to chemical analysis. Of the neutral ^{13}N-NA components, only glutamate and urea or neutral amino acids were detected. Of the cationic components, only NH_4^+ and glutamine were found. The presence of urea in the intestinal extracts was confirmed by $^{13}NH_4^+$ production upon incubation of the extracts with urease. At 25 to 30 minutes after $^{13}NO_2^-$ administration, the intestinal ^{13}N-NA consisted of 59 percent (50 to 67 percent) glutamate, 36 percent (28 to 44 percent) NH_4^+, 3.8 percent (2.3 to 5.8 percent) glutamine, and 1.8 percent (1.2 to 2.1 percent) urea and neutral amino acids.

Under our chromatographic conditions, dimethyl-, dipropyl-, and diphenylnitrosamines have elution times different from the ^{13}N species found in plasma and in the intestines. Our limit of detection is about 0.1 percent of the total chromatographed radioactivity. This corresponds to approximately 0.01 percent of the total instilled activity. No ^{13}N-labeled components were detected at the elution positions of these simple nitrosamines. Thus, these potential nitrosation products are not synthesized at rates comparable to assimilatory products in vivo under our "no carrier added" conditions. However, we cannot rule out minor formation of these or other potential nitrosation products.

In summary, $^{13}NO_2^-$ introduced into the respiratory tract at dosages below the level of pharmacological perturbation enters the intestines as both NO_2^- and NO_3^-. Within 30 minutes, the intestinal fraction of activity accounts for 0.1 to 0.2 of the WBA in CV mice. About 80 percent of this intestinal activity in both CV and SPF mice is found in reduced forms as NH_4^+, amino acids, and urea. Simple ^{13}N-labeled nitrosamines were not detected by HPLC in animals fed a normal diet. In contrast, GF and exenterated CV mice produced no ^{13}N-NA in any of the tissues examined. The metabolism of $^{13}NO_2^-$ and $^{13}NO_3^-$ in CV and SPF mouse intestines is thus rapid and chemically reductive. These observations do not support arguments for nitrification, which is oxidative, in the intestines of mammals (*20*).

These results relate to the prediction and assessment of human health risk associated with the inhalation of nitrogenous compounds that can form NO_2^- in vivo. In an evaluation of biological response data, Dawson and Schenker showed that a 1-hour inhalation of NO_2 at 0.1 part per million (ppm) significantly decreases the threshold for asthmatic provocation in predisposed humans (*21*). An NO_2 concentration of 0.1 ppm, which appears to be near the threshold for adverse physiological response, can result in an inspiration of approximately 40 ng kg^{-1} min^{-1} in humans (*22*). Recent chemical studies indicate that such concentrations of NO_2 may form nitrous acid (which is converted into NO_2^- at physiological *p*H) by hydrogen abstraction from pulmonary lipids (*23*) rather than NO_2^- and NO_3^- by disproportionation (*24*). An in vitro study with perfused rat lungs exposed to NO_2 showed that NO_2^- was the only product in the absence of erythrocytes (*25*). This result is consistent with prior observations that the concentration of ^{13}N in the blood of monkeys who inhaled $^{13}NO_2$ rises in proportion to the amount inhaled (*26*) and that ^{13}N from $^{13}NO_2^-$ rapidly leaves the lung as the ion (*11*).

Our measurements in mice indicate an exponential destruction of NO_2^- by the combined mechanisms of reduction and oxidation, with a biological half-period (time needed for half of a reaction to be completed) of about 7 minutes (*27*). If these metabolic studies in mice are appli-

Table 1. Summary of the ^{13}N-labeled product distribution in various tissues after intratracheal instillation of $^{13}NO_2^-$ in mice. Fifteen microliters of $^{13}NO_2^-$ was intratracheally instilled without added carrier. The mice were killed as described in (*11*) 12 to 31 minutes after instillation. Selected tissues were then homogenized in saline and centrifuged for 60 seconds at 12,000*g*, and the supernatant was filtered through 0.5-μm disposable filters prior to chromatographic analysis; ND, not detected.

Tissue	Fraction of WBA*	Percentage of tissue ^{13}N activity as†		
		Nonanionic	NO_2^-	NO_3^-
	Four conventional mice (12 to 31 minutes)			
Plasma	0.044 (0.032 – 0.059)	3.9 (3.5 – 4.2)	6.8 (5.2 – 8.8)	89 (87 – 91)
Intestine	0.122 (0.111 – 0.134)	84 (78 – 88)	0.18 (0.08 – 0.40)	16 (11 – 22)
Liver	0.070 (0.064 – 0.076)	33 (30 – 36)	ND	67 (64 – 70)
Stomach	0.020 (0.019 – 0.021)	6.8 (5.1 – 9.0)	3.2 (1.7 – 6.0)	90 (85 – 93)
Urine	< 0.03	7.8 (7.5 – 8.1)	1.4 (1.0 – 2.0)	90 (87 – 93)
Others‡	0.736 (0.702 – 0.767)			
	Two exenterated conventional mice§ (6 and 25 minutes)			
Plasma		ND	67	33
Plasma		ND	27	72
	One penicillin-treated mouse¶ (25 minutes)			
Plasma		ND	13	86
	Three germ-free mice (12 to 34 minutes)			
Plasma		ND	14 (10 – 18)	86 (82 – 90)
Intestine		ND	28 (23 – 34)	72 (66 – 77)
Liver		ND	2.2 (1.0 – 4.8)	98 (94 – 99)
	Three specific pathogen–free mice (12 to 29 minutes)			
Plasma		3.0 (2.6 – 3.5)	20 (15 – 25)	77 (71 – 82)
Intestine		85 (72 – 92)	8 (7 – 10)	5 (1 – 18)
Liver		14 (9 – 23)	11 (7 – 17)	72 (70 – 74)
Urine		5 (4 – 7)	4 (3 – 5)	90 (86 – 93)

*Given as the mean (and asymmetric error interval). †The percentage of recovered label in the indicated form (nonanionic, NO_2^-, or NO_3^-) in the extracted tissue is given as the mean (and asymmetric error interval). The measure of the central tendency and dispersion for the chromatographically determined product activity fractions that are bounded by the fixed margins of 0 and 100 percent was made on the basis of the logit logarithmic transformation (*19*). ‡The fractions of whole body activity of conventional mice in the organs not listed were as follows: lung, 0.017 (0.014 – 0.019); heart, 0.008 (0.007 – 0.009); kidney, 0.023 (0.019 – 0.027); bladder, 0.002 (0.001 – 0.003); spleen, 0.0045 (0.0042 – 0.0048); and carcass, 0.63 (0.58 – 0.67). §These mice were exenterated prior to instillation of $^{13}NO_2^-$. Control mice that were surgically invaded and whose intestines were teased out intact and then replaced yielded results identical to those of untreated BALB/c mice. ¶The drinking water of this mouse was amended with buffered penicillin G (Pfitzerpen) (0.3 g $liter^{-1}$) 24 hours before instillation of $^{13}NO_2^-$.

cable to humans, continuous inhalation of air containing 0.1 ppm NO_2, or concentrations of other nitrogenous compounds giving rise to NO_2^- at equivalent levels, will lead to a concentration of NO_2^- in body fluids and tissues of about 400 ng kg^{-1} (about 30 n*M*) (*28*). Consequently, we suggest that continuous exposure to atmospheric concentrations of NO_2 or other NO_2^- precursors below 0.1 ppm are unlikely to produce an extrapulmonary health risk (for example, by production of carcinogenic nitrosamines). By comparison, a continuous exposure to more than 100 ppm NO_2 would be required to produce gastric concentrations of NO_2^- comparable to the transient micromolar values associated with the ingestion of a meal containing 2 to 3 mg of NO_2^-. The in vivo concentrations of NO_2^- that may saturate the "normal" metabolic pathways are still unknown.

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28. $(d[NO_2^-]/dt) = -k[NO_2^-]$, which is equal to the input rate. Thus, the equilibrium $[NO_2^-]$ is ~ 400 ng kg^{-1}.
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Diffusion Coefficients of Respiratory Gases in a Perfluorocarbon Liquid

Abstract. *Although great quantities of respiratory gases dissolve in a perfluorocarbon liquid used to formulate artificial blood, their diffusion rates in this liquid do not exceed those in water.*

Some liquid perfluorocarbons can dissolve far greater quantities of gases than other liquids at comparable pressure (*1*). They do not react with the gases in solution; the high energy content of the C–F bonds [approximately 120 kcal/mole (*2*)] accounts for their lack of reactivity (*3*) and is, in part, also responsible for their lack of toxicity.

Aqueous dispersions of perfluorocarbons stabilized by nonionic detergents have been formulated as possible blood substitutes (*4*), for clinical infusion (*5*), or for the perfusion of isolated organs destined for transplantation (*6*). The pure compounds find another promising application in liquid barrier filters (*7*), highly efficient devices that permit gases to pass a continuous liquid phase by diffusion while capturing all particulate contaminants carried in them.

Table 1. Diffusion coefficients of respiratory gases in perfluorotributylamine at 22°C. The last column shows the mean standard deviation of experimental points, grouped by time and diffusion distance, from theoretical values.

Gas	Diffusion coefficient (cm^2 sec^{-1})	Standard deviation (percent)
CO_2	1.3×10^{-5}	2.7 (N = 7)
N_2	1.4×10^{-5}	2.8 (N = 8)
O_2	2.0×10^{-5}	2.4 (N = 9)

Discussions of the possible value of perfluorocarbon preparations as blood substitutes always refer to their enormous gas-carrying capacity. Correlations exist between the solubility of gases in fluorocarbon liquids and the boiling points, densities, molecular weights, viscosities, and surface tensions of the liquids (*8*). However, the solubility is only a measure of solute uptake and does not distinguish between the solute molecules freely available in the solvent and those irreversibly bound to it; it is not a parameter defining the gas transfer capacity of a liquid. As both the solubility and the passage of gases are important functional criteria in all the applications given above, it would appear appropriate to state not only the solubility but also the

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