Carcinogenicity of N-Nitrosomethyl(2-oxobutyl)amine and N-Nitrosomethyl-(3-oxobutyl)amine in Syrian Hamsters with Special Reference to the Pancreas

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ABSTRACT

Studies with oxidized derivatives of N-nitrosodi-n-propylamine suggested a structure-activity relationship between pancreatic cancer induction in Syrian hamsters and position and degree of nitrosamine oxidation. To elucidate the importance of the position of the oxidized substituent relative to the N-nitroso group in pancreatic carcinogenesis, we compared the toxicity and carcinogenicity of two substituted methylbutylnitrosamines. N-Nitrosomethyl(2-oxobutyl)amine (M-2-OB) and N-Nitrosomethyl(3-oxobutyl)amine (M-3-OB) were given in equitoxic doses to male and female Syrian hamsters. The 50% lethal doses for M-2-OB and M-3-OB in males and females, respectively, were 92 and 160 and 705 and 810 mg/kg body weight. M-2-OB, although given in significantly smaller doses (minimum dose, 2.3 mg/kg body weight) than was M-3-OB (minimum dose, 17.6 mg/kg body weight), induced a much broader spectrum of neoplasms (17 tissues), whereas M-3-OB induced tumors in only 5 tissues and had no carcinogenic effect in the pancreas. M-2-OB, however, produced pancreatic ductular-ductal adenocarcinomas in over 90% of the males and 67% of the females, even at the lowest doses (2.3 and 4.0 mg/kg, respectively). Although both compounds caused a similar incidence of morphologically equivalent neoplasms (mostly adenocarcinomas) in the nasal and paranasal cavities, the remaining distribution of affected tissues differed significantly. M-2-OB predominantly affected the lip (epitheliomas, squamous cell carcinomas), liver (cholangiomas and cholangiocarcinomas), and flank organ (epitheliomas, squamous cell carcinomas). The principal target organs for M-3-OB were the cheek pouch (papillomas, squamous cell carcinomas) and trachea (polyps). In contrast to M-2-OB, M-3-OB did not induce renal and urethral tumors. These findings indicate the importance of the 2-oxo group as a prerequisite for the carcinogenicity of methylalkylnitrosamines in the hamster pancreas; however, a methyl group in one aliphatic chain, α to the N-nitroso function, appears to cause the molecule to lose its selectivity for the pancreas.

INTRODUCTION

All of the pancreatic carcinogens in Syrian hamsters, including BHP,3 BOP, N-nitrosobis(2-oxoethyl)amine, N-nitroso-2,6-di-methylmorpholine, N-nitroso-2-methoxy-2,6-dimethylmorpholine, N-nitrosobis(2-oxobutyl)amine, and N-nitroso(2-oxobutyl)(2-oxopropyl)amine, possess or can be metabolized to dialkyl nitrosamines with 2-hydroxy or 2-oxo groups in both propyl and butyl chains (2, 7, 13, 17, 18, 22–25, 28, 29). The potent pancreatic carcinogenicity of MOP (21), the proposed proximate pancreatic carcinogen (12, 25), indicated that a methyl group α to the N-nitroso function and the presence of a keto group in the aliphatic chain are essential for pancreaticotropic effect. To further elucidate a relationship between structure of the carcinogen and organotropism, we examined the carcinogenicity and toxicity of M-2-OB and M-3-OB in Syrian golden hamsters.

MATERIALS AND METHODS

Chemicals

M-2-OB. To a solution of 84 ml of 12 N hydrochloric acid and 56 ml of water were slowly added 13.7 g (87.3 mmol) of N-methyl-N-2-oxobutylpropionamide (33). This mixture was refluxed for 24 hr under nitrogen and flash-evaporated to a wet solid, which was dissolved in 30 ml of water and cooled to 5°, after which 7 g (103 mmol) of sodium nitrite were added slowly. After 1 hr of stirring, the mixture was extracted with ethyl ether (3 x 75 ml), dried (Na2SO4 and NaHCO3), filtered, and concentrated to give 9.95 g (88%) of a yellow oil.

C9H12NO2

Calculated: C 46.14, H 7.74, N 21.52
Found: C 45.92, H 7.73, N 21.18

Proton NMR (CDCl3) (major conformer, 51%): δ 1.08 (q, 3H, O—CH3), 2.48 (t, 2H, γ—CH2), 3.85 (s, 3H, N—CH3), 4.32 (s, 2H, N—CH2); (minor conformer, 49%): δ 1.14 (q, 3H, δ—CH3), 2.57 (t, 2H, γ—CH2), 3.07 (s, 3H, N—CH3), 5.01 (t, 2H, N—CH2). Assignment of proton resonances and hence conformational assignments of M-2-OB were carried out using standard NMR techniques. It was assumed that the anisotropic effect of the nitroso group would shield groups which are syn to the nitroso function (8). The major conformer had the nitroso group syn to the 2-oxobutyl group. IR (CCl4): 1729 cm⁻¹ (νC = 0). UV (H2O): λmax 232 nm, ε = 6940; λmax 341 nm, ε = 91.2.

M-3-OB. To an ice-cold solution of 18.5 g (0.18 mol) of 1-methylamino-3-butanol in 200 ml of H2O were added 20 g (0.30 mol) of sodium nitrite. The solution was acidified to pH 3 with 5 N hydrochloric acid, stirred overnight, extracted with ethyl acetate, dried, and flash-evaporated. The resultant syrup was dissolved in acetone and cooled in ice, and 40 ml Jones’ reagent (11) were added until the orange color persisted. After 1 hr of stirring, isopropyl alcohol was added until the solution remained green. The precipitate was filtered, and the solution was flash-evaporated. The residue was dissolved in water, extracted with chloroform, dried, and flash-evaporated.

The crude product was purified on 400 g silica gel eluting with hexane-ethyl ether. Evaporation of the desired fractions gave 14.5 g (70% yield) of the nitrosamine as a yellow oil.
Proton NMR (CDCl₃) (major conformer 66%): δ 0.03 (s, 3H, ß—CH₃), 2.83 (t, 2H, ß—CH₂), 2.86 (s, 3H, N—CH₃), 4.17 (t, 2H, ß—CH₂); (minor conformer, 33%): δ 1.95 (s, 3H, ß—CH₃), 2.53 (t, 2H, ß—CH₂), 3.24 (s, 3H, N—CH₃), 3.57 (t, 2H, ß—CH₂). Assignment of proton resonances of M-3-OB was carried out as described for M-2-OB. Major conformer has the nitroso group syn to the A/-methyl group. IR (CCl₄): 1726 cm⁻¹ (νC = O). UV (H₂O): λₘₚ 230 nm, ε = 5800; λₘₚ 337 nm, ε = 80.3.

Animals

Outbred Syrian golden hamsters from the Eppley colony were housed in groups of 5 by sex in plastic cages on granular cellulose bedding (Bed-O-Cobs; Anderson Cob Division, Maumee, Ohio) under standard laboratory conditions. They were given Wayne pelleted diet (Allied Mills, Chicago, Ill.) and water ad libitum. Animals were 8 to 10 weeks old at the beginning of experiments, and their average weight was 118 ± 12 (S.D.) g (males) and 114 ± 14 g (females). The LD₅₀'s of M-2-OB and M-3-OB were calculated by the method of Weil (32). Single s.c. injections of various doses, differing by factors of 2, were given to groups of 5 females and 5 males per dose. Hamsters that survived the acute toxic effect of the carcinogens were kept until their spontaneous death (Group A).

For chronic carcinogenicity testing, hamster groups (Group B), composed of 15 females and 15 males each, were treated s.c. weekly for life with either M-2-OB (Group Bl) or M-3-OB (Group Bll) at doses corresponding to 1/20, 1/40, or 1/60 of the LD₅₀. Control hamsters (30 females, 30 males) received weekly s.c. injections of vehicle.

RESULTS

M-2-OB. The LD₅₀'s of M-2-OB were 92 and 160 mg/kg body weight in males and females, respectively. Doses of 200 and
400 mg/kg body weight were lethal and killed all but one hamster during the second and third posttreatment days. Signs of acute toxicity included cell degeneration of nasal olfactory epithelium, liver, kidneys, and intestines and hemorrhages of thoracic and abdominal tissues. All but 2 surviving hamsters developed tumors at multiple sites (Table 1). Females did not receive the 50-mg/kg body weight dose because of their high survival rate at 100 mg/kg body weight.

Nearly all hamsters treated weekly for life had multiple neoplasms (up to 17 tumors/animal; an average of between 3.3 and 9.3 tumors/tumor-bearing hamster) in the same or different tissues (Table 1). Carcinogen-treated hamsters showed a mild to moderately suppressed body weight gain compared to controls.

Tumor sites varied in Groups A and B (Table 1). However, the morphological patterns of induced lesions were similar in both the A and the B groups.

Nasal and paranasal cavity neoplasms were mostly adenocarcinomas of the posterior region, less frequently, papillomas in the anterior region, and least often, mucoepidermoid tumors of the anterior region. The histological appearance of these neoplasms was similar to that reported earlier by us (20).

Laryngeal and tracheal tumors were all papillary polyps, as described previously (23), except for a single squamous cell carcinoma of the larynx in a Group B female. Pharyngeal neoplasms were papillomas, which generally were multiple.

Neoplasms arising from the lips were, with decreasing frequency, trichoepitheliomas, papillomas, and squamous cell carcinomas; the latter had metastases to the cervical lymph nodes in 7 Group B female hamsters. The location and morphology of these neoplasms were similar to those described previously (19, 26). Focal and multifocal hyperplasia of surface epithelium and of piosebaceous glands was found in nearly all hamsters with or without tumors.

Intestinal tumors were found in the cecum and/or rectum, except for one neoplasm (polyp) located in the ileum. All colonic lesions were either carcinomas in situ and/or invasive adenocarcinomas.

Hepatic tumors were mostly cholangiomas, less frequently cholangiocarcinomas, and there were a few hepatocellular adenomas, hemangioendotheliomas, angiosarcomas, and hepatocellular carcinomas. Gall bladder and common duct tumors were polyps, with the exception of one gall bladder carcinoma.

Pancreatic neoplasms in Group A consisted of one ductular adenoma and one ductular adenocarcinoma; whereas in Group B, most lesions were ductular-ductal adenocarcinomas. The carcinoma incidence was similarly high in males of all dose groups (93, 73, and 73% in the low-, medium-, and high-dose groups, respectively), whereas in females the incidence was lower in the low-dose group (47%) than in the medium-dose group (53%) and high-dose group (67%). Carcinomas were multifocal (up to 7/animal) in all hamsters and averaged between 1.2 and 2.4 lesions/hamster. Ductular-ductal carcinomas in situ appeared in greater numbers (up to 10 lesions/animal). The tumors varied in diameter from those of microscopic size to 30 mm; they were mostly over 10 mm in diameter and presented
distant metastases (in lymph nodes, liver, and occasionally in the lungs).

Renal neoplasms were, with decreasing frequency, tubular adenomas, tubular adenocarcinomas, hemangiomas, and mixed mesenchymal epithelial lesions that often occurred simultaneously.

Urethral and vaginal tumors were papillomas, and there was one urethral squamous cell carcinoma.

Lesions of the male flank (scent) organ were epitheliomas up to 20 mm in diameter [described as chaeotepitheliomas (9, 10)] and 3 squamous cell carcinomas. All but 2 tumors were bilateral. Focal hyperplasia of the epidermis and scent glands was found in all hamsters with or without tumors.

Neoplasms of other sites are summarized in Table 1. Of these, thyroid follicular adenomas, lung adenomas, tracheal polyps, and urinary bladder papillomas were probably induced lesions, whereas the remainder were within the range of spontaneous neoplasms in this hamster strain.

M-3-OB. The LD₉₀ of M-3-OB was 705 mg/kg body weight for males and 810 mg/kg body weight for females. Hamsters treated with M-3-OB (1000 mg/kg) died within the second and third day and exhibited the same response in terms of toxic effects as those described for M-2-OB-treated hamsters. Among 14 surviving hamsters, only 6 developed tumors (Table 2).

Treatment did not affect body weight (except in males of Group A treated with the highest dose) but shortened survival in Groups A and B compared to that in controls (Table 2). Whereas tumor incidence in Group A hamsters was generally low, almost all Group B hamsters developed neoplasms. In Groups A and B, the tumor spectrum was narrow and the multiplicity small, not exceeding 5 neoplasms/animal (on the average, there were between 0 and 4.2 tumors/tumor-bearing hamsters). Single carcinogenic doses did not affect a specific target tissue. However, chronic M-3-OB exposure preferentially affected the respiratory tract, but no dose-response relationship was seen with regard to incidence or multiplicity. Most of the neoplasms were adenocarcinomas of the posterior nasal region, with one metastasis to the lungs. Tracheal and laryngeal neoplasms were mostly solitary polyps; females treated with the lowest dose developed a significantly higher tumor incidence than did corresponding females treated with M-2-OB.

The cheek pouch neoplasms, which were not found in M-2-OB-treated hamsters, were multiple (1 to 3), small nodules presenting either squamous cell papillomas or squamous cell carcinomas with one metastasis to the submandibular lymph nodes. Hyperplasia and hyperkeratosis of the cheek pouch mucosa were diagnosed in many hamsters with or without neoplasms and lip papillomas were diagnosed in 2 male hamsters. Neoplasms of the pharynx and stomach were papillomas, those of the liver were hemangioendotheliomas and 1 cholangioma, and those of the colon were either polyps or, more frequently, adenocarcinomas. The latter were seen only in Group B hamsters, and their incidence was significantly less than those induced by M-2-OB. Carcinomas, often multiple, were located either in the cecum or rectum. Two of the rectal carcinomas developed in females, and the remaining 12 were found in males. Hyperplasia of mucosal epithelium in the cecum and rectum was seen in many hamsters, with or without colorectal neoplasms.

Common duct, pancreatic, and renal tumors did not occur, and significantly fewer gall bladder and vaginal neoplasms developed compared to observations in hamsters treated with M-2-OB. All other tumors in Table 2, except for s.c. hemangiomas and carcinoma in situ of the ileum, should be considered spontaneous diseases.

**DISCUSSION**

The present experiment demonstrated that M-2-OB was a pancreatic carcinogen whereas M-3-OB was not, a finding that clearly points to the importance of the 2-oxo group in pancreatic carcinogenesis. Like MOP (21), M-2-OB induced a high incidence of pancreatic ductal and ductular adenocarcinomas within a relatively short time. However, when we consider the broad spectrum of M-2-OB-induced neoplasms and the fact that single doses of the compound were not as effective in inducing pancreatic neoplasms as those of MOP (21), N-nitrosobis(2-oxobutyl)amine, and N-nitroso(2-oxopropyl)(2-oxobutyl)amine (24), M-2-OB appears to be less selective for the pancreas.

Among the pancreatic carcinogens thus far tested, BOP is the most specific and selective (15, 30). Recent studies have shown that BOP appears to be selectively taken up by the hamster pancreas rather than the liver (another target tissue of BOP), since higher concentrations of BOP and its metabolites, HPOP, BHP, and MOP, are present in the pancreas relative to the liver (12). The hamster pancreas also appears to be more efficient in metabolizing BOP to MOP, the proposed proximate carcinogen. When the effects of M-2-OB were compared with those of MOP, several points appear noteworthy. The butyl compound was about one-fourth as toxic as was the propyl homologue, a finding in accord with the general experience in dialkylnitrosamine carcinogenesis; i.e., a reverse relationship exists between toxicity and length of the alkyl chains (1, 34). When equitoxic doses were compared, M-2-OB caused a larger tumor spectrum (inducing tumors in 17 tissues) than did MOP (which affected at most 5 tissues), despite the longer survival time of MOP-treated hamsters (up to 19 weeks). This difference cannot be related to the larger M-2-OB doses used when comparing results of the lowest M-2-OB dose, which corresponded to the highest MOP dose. Studies on an equimolar basis, however, would be more adequate to define differences in carcinogenicity. Common to both compounds was the induction in similar incidences of morphologically equivalent neoplasms in the upper and lower respiratory tract (lungs excluded) and the liver. This pattern of tumor induction in the hamster respiratory epithelium appears similar to those seen with nitrosamines having at least one N—CH₃ group (23). On the other hand, significantly more tumors were induced in the lips, colon, and flank organ by M-2-OB than by MOP, while (unlike the findings with M-2-OB) no urethral papillomas were detected after MOP treatment. This is consistent with the known affinity of the butyl nitrosamines, including N-nitrosobis(2-oxobutyl)amine and N-nitroso(2-oxopropyl)(2-oxobutyl)amine, for the urothelial epithelium (24). In this context, the failing carcinogenic effect of M-3-OB on the lower (as well as the upper) urinary tract argues against the view that metabolism of the nitrosomethylalkylamines with even-numbered chains is qualitatively similar and correlates with their carcinogenicity in the urothelium (31). Our results are consistent with those of Okada et al. (14), who reported that among the urinary bladder tumorinites those related to N-nitrosodi-n-butylamine, N-nitroso-n-butyl-n-(3-hydroxybutyl)amine, and N-nitroso-n-butyl-n-(3-oxobutyl)amine were not bladder carcinogens. Possibly, the presence of a 3-oxo or 3-hydroxy group prevents generation of...
Table 2
Carcinogenicity of M-3-OB in Syrian hamsters treated once (Group A) or weekly for life (Group B)

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg body wt)</th>
<th>No. of hamsters treated once (wk)</th>
<th>Body wt (g)</th>
<th>No. of tumor-bearing animals</th>
<th>Av. no. of tumors/tumor-bearing animal</th>
<th>Nasal cavities</th>
<th>Larynx</th>
<th>Trachea</th>
<th>Cheek pouch</th>
<th>Lip</th>
<th>Pharynx</th>
<th>Fore-stomach</th>
<th>Liver</th>
<th>Colon</th>
<th>Others</th>
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<td>5</td>
<td>46 ± 11(^a)</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>1</td>
<td>1 (20)</td>
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<td>35 ± 4</td>
<td>63 ± 8</td>
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<td>1.7</td>
<td>1 (33)</td>
<td>0</td>
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<td>1 (33)</td>
<td>0</td>
<td>B(^c) 7</td>
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<td></td>
<td>F</td>
<td>250</td>
<td>5</td>
<td>47 ± 10</td>
<td>105 ± 17</td>
<td>2 (40)</td>
<td>1.5</td>
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<td>0</td>
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<td>C(^c) 20</td>
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<td>D(^c) 20</td>
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<td>F</td>
<td>81</td>
<td>15</td>
<td>28 ± 6</td>
<td>109 ± 30</td>
<td>14 (93)</td>
<td>2.3</td>
<td>12 (92)</td>
<td>2 (13)</td>
<td>7 (47)(^d) 9 (60)(^e)</td>
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<td>78 ± 28</td>
<td>15 (100)</td>
<td>3.8</td>
<td>15 (100)</td>
<td>2 (13)</td>
<td>8 (53)(^d) 9 (60)(^e)</td>
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<td>106 ± 21</td>
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<td>14 (100)</td>
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<td>104 ± 28</td>
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<td>12 (86)</td>
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<td>99 ± 22</td>
<td>14 (93)</td>
<td>2.8</td>
<td>8 (53)</td>
<td>4 (27)</td>
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<td>15</td>
<td>55 ± 17</td>
<td>96 ± 24</td>
<td>3 (20)</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
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<td>K(^c) 7</td>
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\(^a\) Average ± S.D.
\(^b\) Numbers in parentheses, percentage.
\(^c\) A, gall bladder polyps; B. Cowper's gland adenoma; C, thyroid follicular adenoma; D, vagina papilloma; E, malignant lymphoma; F, ileal carcinoma in situ; G, testicular mesothelioma; H, peritoneal mesothelioma; I, s.c. hemangiomata; J, adrenocortical cell adenoma; K, parathyroid adenoma; L, pancreatic ductal adenoma; M, nodal plasmacytoma.
\(^d\) Higher tumor incidence (p < 0.05) compared to corresponding tumors induced by M-2-OB.
BOP, a proposed proximate carcinogen for the pancreas (21) and urinary bladder (31). However, since BOP similarly did not affect rat urothelium (14), some other factors must be involved.

M-3-OB was 5 to 10 times less toxic and less carcinogenic (smaller tumor spectrum) than was M-2-OB, despite the longer survival of the M-3-OB-treated hamsters. This difference is less likely to be related to the small number of animals used, since the carcinogenicity of M-3-OB and M-2-OB for the nasal cavity was comparable. Whereas the incidence of tracheal polyps was significantly higher, that of the liver was significantly lower after M-3-OB than after M-2-OB; and no gall bladder, common duct, and urinary tract tumors were induced by M-3-OB.

A striking difference between the carcinogenicity of M-2-OB and M-3-OB was their effect on buccal and flank epithelium. Lip and flank organs were 2 major target tissues for M-2-OB, whereas M-3-OB induced a few lip and no flank organ tumors. Conversely, cheek pouch neoplasms developed only after M-3-OB. The induction of flank (scent) organ epitheliomas and carcinomas by M-2-OB is of particular interest, since these neoplasms are known to be hormone-related lesions (9, 10). The potency of the related compounds BOP, BHP, and HPOP to induce tumors in other sex hormone-dependent tissues in hamsters, e.g., the ovaries, kidneys, and vagina (18, 22, 28), and in rats (the prostate and uterus) (16, 27) may indicate that sex hormones influence the effects of these carcinogens.

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