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Mammary Tumorigenic Effect of a new Nitrosourea, 1,3-Dibutyl-1-nitrosourea(B-BNU), in Female Donryu Rats*

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1,3-Dibutyl-1-nitrosourea (B-BNU) was synthesized by nitrosoation of 1,3-dibutylurea, prepared by reaction of butyl isocyanate with butylamine in toluene, with an aqueous solution of sodium nitrite and 25% sulfuric acid at 0—3°C, treated with petroleum ether to eliminate almost all of unchanged butylurea and followed by columnchromatography on Kiesel gel with chloroform acetone (7: 1, vol/vol). The identifications were made by UV, IR, NMR and element analysis.

Four groups of five-year-old female Donryu rats, each of which consisted of 36, were maintained on the basal diet CE-2 and tap water until they were 11 weeks old, and thereafter, were given continuously 400, 200, 100 or 0 ppm solution of B-BNU respectively as drinking water.

The first autospy of a rat with tumor was made at the 236th experiment day, and 17, 12, 10 and 11 rats died before that time in group 1, 2, 3 and 4 respectively, which were excluded from the data.

Tumors induced in various organs in each group were listed in Table 1.

Mammary tumors were induced in 79—83% of rats, followed by hematopoietic

Table 1 Tumors in various organs induced by continuous oral administration of B-BNU in Donryu rats

Group	Concentr. of B-BNU (ppm)	No. of rats examined	No. of rats with tumors	Av. survival period (days ± SD)	No. of rats with tumors in(%)				
					Mammary glands	Hematopoietic organs	Uterus	Vagina	Others
1	400	19	17 (89%)	350±58	15 (79%)	4 (21%)	2 (11%)	2 (11%)	8[a] (42%)
2	200	24	22 (92%	365±47	20 (83%)	5 (21%)	3 (13%)	1 (4%)	6[b] (25%)
3	100	26	23 (88%)	386±53	21 (81%)	3 (12%)	6 (23%)	3 (12%)	4[c] (15%)
4	0	25	10 (40%)	479±72	8 (32%)	1 (4%)	0	0	1[d] (4%)

a) Three each in thyroid gland and jaw, 1 each in ovary and brain

b) One each in thyroid gland, ovary, liver, retroperitoneum, subcutaneous tissue, and ear duct

c) One each in jaw, ovary, medulla oblongata, and colon

d) One in brain

Table 2. Histological types of mammary tumors in each group

Group	No. of rats and nodules					
	Fibroadenoma		Adenoma		Adenocarcinoma	
	Rats	Nodules	Rats	Nodules	Rats	Nodules
1	11	30	3	5	4	4
2	19	65	4	4	7	8
3	21	81	6	10	1	1
4	5	9	4	6	0	0

neoplasms, 12—21%, uterine, 11—23% and vaginal tumors, 4—12%. Other tumors were infrequent, and the incidence was lower than 16% in each group. In the control group, tumors were found only in mammary glands, 32%, and hematopoietic organs and brain, 4% each.

Histological types of mammary tumors in each group was listed in Table 2. Fibroadenomas were most common, followed by adenomas and adenocarcinomas.

Various types of leukemia were found, but the relationship between the daily dose of B–BNU and cell type of induced leukemia was not determined.

Uterine tumors(11 rats)were classified to adenomas (2), myomas(6)and myosarcomas(3).

In vaginal tumors, papillomas and non-epithelical tumors were found in three rats respectively.

Mammary tumors has been induced by many chemicals in rats, among which 7,12-dimethylbenz[*a*]anthracene (DMBA) is the most potent inducing mammary tumors in 100% of rats. Now, B–BNU was found to be the strongest carcinogen among N-nitrosoureas tested to induce mammary tumors in 80% of female Donryu rats, and is comparable to DMBA. However, B–BNU is not considered to be a direct carcinogen because almost no tumors developed in the digestive tract in the experimental groups. In addition to this, the doseeffect relationship was not clearly determined, and even the lowest dose level resulted in the development of tumors in similar level as in the highest dose group.

In general, in our experiment, survival period of rats with mammary tumors was longer than those with other types of tumors. The average survival period of rats with mammary tumors and number of nodulas induced were different in treated groups; the former was shorter in the higher dose groups and longest in non-treated group, and, on the other hand, the latter was smaller in the higher dose groups and larger in the lower dose groups.

Based on the results in a series of our study on carcinogenic effect of various N-nitrosoureas, it can be said that butylnitrosoureas have both leukemogenic and mammary-tumorigenic activities, and the former effect is much higher in 1-butyl-1-nitrosourea and 1-butyl-3,3-dimethyl-1-nitrosourea and the latter is much stronger in B–BNU.

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