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Similar, Potent Tumor-promoting Activity of All Isomers of Teleocidins A and B in a Two-Stage Carcinogenesis Experiment on the Skin of CD-1 Mice[1]

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ABSTRACT

Teleocidin, isolated from mycelia of *Streptomyces mediocidicus* is a mixture of two teleocidin A isomers with molecular weights of 437 (A-1 and A-2) and four teleocidin B isomers with molecular weights of 451 (B-1, B-2, B-3, and B-4). Previously we found that each purified isomer of teleocidins A and B had approximately the same activity as teleocidin in an irritant test on mouse ear, in inductions of ornithine decarboxylase in mouse skin and adhesion of human promyelocytic leukemia (HL-60) cells, and in inhibition of the specific binding of [^{3}H]-12-*O*-tetradecanoylphorbol-13-acetate to a mouse skin particulate fraction. This paper reports the strong activation of protein kinase C *in vitro* by each isomer of teleocidins A and B at a concentration of 1 μg/ml. Detailed studies on the potent tumor promoting activities of the two teleocidin A isomers and four teleocidin B isomers in a two-stage carcinogenesis experiment on mouse skin are also reported, including histological findings on the tumors. Treatment of mice with 100 μg of 7,12-dimethylbenz(*a*)anthracene and then 2.5 μg of any one of the six isomers of teleocidins A and B twice a week induced tumors in 80.0 to 91.7% of the mice with 2.8 to 5.2 tumors/mouse in week 30. Scarcely any tumors developed in groups treated with 7,12-dimethylbenz(*a*)anthracene or any one of the isomers of teleocidins A or B alone. The percentages of incidences of mice bearing papillomas and carcinomas in the six groups treated with 7,12-dimethylbenz(*a*)anthracene plus one isomer of teleocidins A or B were 90.9 to 98.3% and 1.7 to 9.1%, respectively. These results indicate that all of the isomers of teleocidins A and B have potent tumor promoting activity on mouse skin, irrespective of the structural differences between teleocidins A-1 and A-2, and among the four isomers of teleocidin B.

The structure-activity relationship of teleocidins A and B is discussed on the basis of our recent results. Based on the structures of related compounds, we propose a revised numbering system for compounds of the teleocidin class.

INTRODUCTION

The new class of tumor promoters, the teleocidin class, is structurally unrelated to phorbol esters and aplysiatoxins (1, 2). The known tumor promoters of the teleocidin class are dihydroteleocidin B, teleocidin, lyngbyatoxin A, des-*O*-methylolivoretin C, (−)-indolactam-V and *N*-geranyl-(±)-indolactam-V (3–7). Teleocidin, isolated from *Streptomyces mediocidicus* (1, 2, 8), was as strong a tumor promoter as TPA and aplysiatoxin in a two-stage carcinogenesis experiment on mouse skin (1–3, 9). The teleocidin used for this experiment was a mixture of the two teleocidin A isomers with molecular weights of 437 and four teleocidin B isomers with molecular weights of 451. The two teleocidin A isomers were named teleocidins A-1 and A-2 in order of their elution on HPLC[3] and the four teleocidin B isomers were similarly named teleocidins B-1 to B-4 (2, 10). Teleocidin A-1 is identical with lyngbyatoxin A, which was isolated from the Hawaiian blue-green alga *Lyngbya majuscula* (5, 10, 11). Lyngbyatoxin A showed similar tumor promoting activity in a two-stage carcinogenesis experiment on mouse skin to that of teleocidin, the mixture of teleocidins A and B (5). The next objective of our research was to study whether the other teleocidin A isomer, A-2, and the four teleocidin B isomers were equally potent tumor promoters. The two teleocidin A isomers and three of the teleocidin B isomers have been purified and used for further experiments. However, teleocidin B-1 has not been used experimentally because of its limited availability due to its low content in *S. mediocidicus*. We previously reported the biological and biochemical activities of the two teleocidin A isomers, A-1 and A-2, and three of the teleocidin B isomers, B-2 to B-4 and the percentages of tumor-bearing mice in week 14 of tumor promotion with these compounds (10). Subsequently, teleocidin B-1 was found to be identical to des-*O*-methylolivoretin B, a demethylated form of olivoretin B, which was isolated from *Streptoverticillium olivoreticuli* (12). Thus, studies on the biological and biochemical activities and tumor promoting activity of teleocidin B-1 could be pursued using des-*O*-methylolivoretin B (6, 13). We found that teleocidin B-1 has specific activities similar to the two teleocidin A isomers and the three other teleocidin B isomers in an irritant test, in inductions of ornithine decarboxylase in mouse skin and HL-60 (human promyelocytic leukemia) cell adhesion, and in inhibition of the specific binding of [^{3}H]TPA to a particulate fraction of mouse skin (13). This paper first describes the similarly strong activations of protein kinase C *in vitro* by all the purified isomers of teleocidins A and B, their detailed results of a two-stage carcinogenesis experiment on mouse skin on the percentage of tumor-bearing mice and average numbers of tumors per mouse through the weeks of tumor promotion, and histological findings on the tumors formed in week 30.

Recently, the absolute structures of the two teleocidin A isomers and the four teleocidin B isomers were elucidated. Based on these results, we present a revision of the numbering system for teleocidins A and B to maintain the same numbers for the common atoms in all these compounds. According to this revised numbering system, we propose the nomenclature (19R)-teleocidin A for teleocidin A-1 and (19S)-teleocidin A for A-2, and C-19, C-25-diastereomers for the four teleocidin B isomers (Fig. 1).

MATERIALS AND METHODS

Chemicals. Teleocidin was isolated from a methanolic extract of *S. mediocidicus* by the procedure described previously (1, 2). Briefly,

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[3] The abbreviations used are: HPLC, high performance liquid chromatography; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; DMBA, 7,12-dimethylbenz(*a*)anthracene.

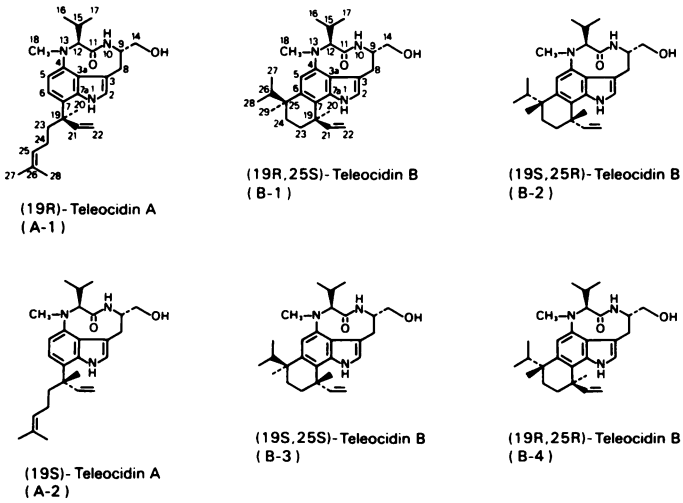

Fig. 1. Structures of isomers of teleocidins A and B with a new numbering system.

teleocidin was first separated into one peak of teleocidin A and two peaks of teleocidin B by HPLC on LS-410 octadecyl silane SIL in 70% acetonitrile. Teleocidin A was then separated into A-1 and A-2 by HPLC on LS-310 SIL in *n*-hexane:chloroform:isopropyl alcohol (85:10:5), and the first and second peaks of teleocidin B were separated into B-1 and B-2, and B-3 and B-4, respectively, by HPLC on LS-410A octadecyl silane SIL in 75% methanol. Olivoretin B was isolated from mycelia of *S. olivoreticuli* and finally purified by HPLC on Radial Pak.-C_{18} in 20% methanol (12). Des-*O*-methylolivoretin B was obtained from olivoretin B by demethylation with BBr_3 in dichloromethane (14). [20-^{3}H]TPA and DL-[1-^{14}C]ornithine monohydrochloride were purchased from New England Nuclear, Boston, MA. [γ-^{32}P]ATP was obtained from Amersham, United Kingdom.

Activation of Protein Kinase C by Each Teleocidin Isomer. Protein kinase C was partially purified from bovine brain by chromatographies on DEAE-cellulose, octyl-Sepharose CL-4B, and finally Ultrogel AcA 44 (15). The specific activity of the partially purified enzyme was 22.5 units/mg protein (16). The assay mixture (0.25 ml) contained 20 μM $CaCl_2$, 7.5 μg of phosphatidylserine, and various concentrations of each isomer of teleocidin with 0.05 unit of partially purified enzyme. Enzyme activity was measured as the incorporation of ^{32}P from [γ-^{32}P]ATP into histone H1 during incubation for 3 min at 30°C (16, 17).

Two-Stage Carcinogenesis Experiment on Mouse Skin. Female CD-1 mice were maintained as described previously (4). Carcinogenesis was initiated by a single application of 100 μg of DMBA dissolved in 0.1 ml of acetone as reported previously (4). From 1 week after initiation, 2.5 μg of each isomer of teleocidins A or B dissolved in 0.1 ml of acetone were applied to the same area of the back twice a week. Control groups were treated with DMBA or an isomer of teleocidin only. Each group consisted of 15 mice. Every 2 weeks throughout the experiment, the hair on the back of the mice was shaved and their body weight was recorded.

Evaluation of Tumor Promoting Activity. The number of tumors of 1 mm or more in diameter was counted every week. The percentage of tumor-bearing mice among survivors and the average number of tumors per surviving mouse were recorded weekly for evaluation of tumor promoting activity. When mice were autopsied at the end of week 30 of tumor promotion, all skin tumors were examined histologically and classified as papillomas or squamous cell carcinomas (4).

RESULTS

Activation of Protein Kinase C *in Vitro* by Individual Isomers of Teleocidins A and B. Protein kinase C is a receptor for the TPA-type tumor promoters TPA, teleocidin and aplysiatoxin (17, 18). The isomers of teleocidins A and B all activated protein kinase C and increased the phosphorylation of histone H1 by protein kinase C, dose dependently at concentrations of 10 ng/ml to 1 μg/ml (data not shown). As shown in Table 1, all isomers of teleocidins A and B showed similar protein kinase activity, being 3.0 to 3.7 pmol/min/1.0 μg of compound. Therefore, the results of activation of protein kinase C *in vitro* by each isomer of teleocidins A and B were consistent with the previous results of the irritant test, and tests on the inductions of ornithine decarboxylase in mouse skin and HL-60 cell adhesion, inhibition of specific [^{3}H]TPA binding (10, 13). The recent and previous results led us to conclude that all the isomers of teleocidins A and B were biologically and biochemically active and showed the same specific activity.

Tumor Promoting Activities of Isomers of Teleocidins A and B. As mentioned previously, experiments on teleocidin B-1 were carried out separately from those on the other isomers (10). Fig. 2*A* shows the percentages of tumor-bearing mice and average numbers of tumors per mouse in six groups treated with DMBA plus one of the isomers of the teleocidins. In this experiment, the first skin tumor of these six groups appeared up to week 9. The percentage of tumor-bearing mice in these six groups ranged from 58.3 to 100% in week 20 but reached plateau values of 80.0 to 91.7% in week 30. No tumors were observed in groups treated with DMBA alone or with any of the isomers of teleocidins A or B alone except teleocidin B-3. In the group treated with teleocidin B-3 alone, one tumor was observed in week 27. Therefore, groups treated with DMBA and any one of the isomers of teleocidins A and B showed high and similar percentages of tumor-bearing mice in week 30.

As Fig. 2*B* and Table 2 show, averages of 2.8 to 5.2 skin tumors/mouse were observed in the six groups in week 30. The tumor yield in the group treated with DMBA plus teleocidin B-1 appeared to be lower than those in the other groups, but minor deviations such as this are often observed in tumor promotion experiments (3, 4).

Table 2 shows histopathological findings on the skin tumors examined in groups treated with DMBA plus one of the isomers of teleocidins A and B. The tumors were classified into two types, papillomas and squamous cell carcinomas. Most of the skin tumors in each group were papillomas, as observed previously in experiments with dihydroteleocidin B, lyngbyatoxin A, and teleocidin (4, 19).

Thus treatments of the six groups with DMBA plus any one of the isomers of teleocidins A and B had similar effects to treatment with DMBA plus teleocidin, especially with the respect to the high percentages of tumor-bearing mice, the high percentage incidences of papillomas, and the low percentage incidences of carcinomas (4). These data clearly indicate that all the isomers of teleocidins A and B are potent tumor promoters in two-stage carcinogenesis on mouse skin.

Table 1 *Activation of protein kinase C by isomers of teleocidins A and B*

Protein kinase C activity was assayed by incorporation of ^{32}P from [γ-^{32}P]ATP into histone H1 during incubation for 3 min at 30°C as described in "Materials and Methods." The activity of a control incubation without teleocidin was 0.3 pmol/min. Each value has been subtracted.

Teleocidin	Activity of protein kinase C (pmol/min/1.0 μg compound)
A-1	3.3
A-2	3.7
B-1	3.7
B-2	3.7
B-3	3.0
B-4	3.0

Table 2 *Tumor-promoting activities of isomers of teleocidins A and B in week 30*

Teleocidin	No. of tumor bearing mice (%)	Av. no. of tumors/mouse	Total no. of tumors	No. of skin tumors examined	Papillomas (%)	Squamous cell carcinomas (%)
A-1	86.6	5.2 ± 1.0[a]	82	76	96.1	3.9
A-2	86.7	4.3 ± 1.3	68	58	98.3	1.7
B-1	86.7	2.8 ± 0.5	42	40	97.5	2.5
B-2	80.0	3.9 ± 0.8	59	55	90.9	9.1
B-3	86.7	4.5 ± 1.0	68	64	93.8	6.2
B-4	91.7	5.0 ± 1.2	60	59	96.6	3.4

[a] Mean ± SE.

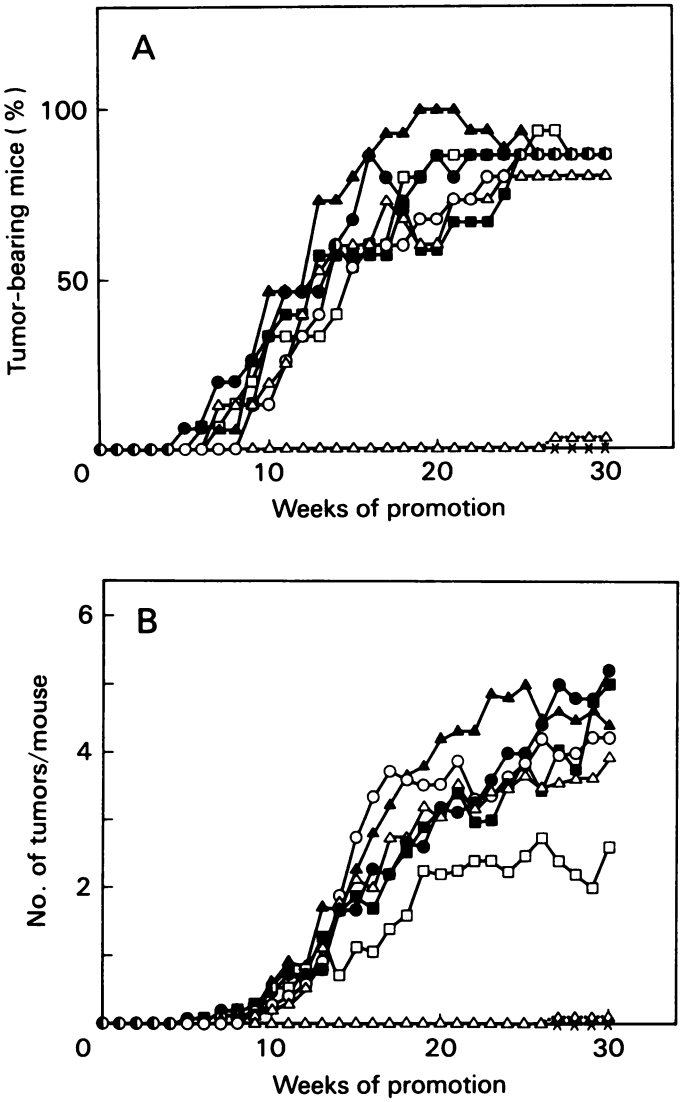

Fig. 2. *A*, percentages of tumor bearing mice in groups treated with DMBA plus teleocidin A-1 (●), DMBA plus teleocidin A-2 (○), DMBA plus teleocidin B-1 (□), DMBA plus teleocidin B-2 (△——△), DMBA plus teleocidin B-3 (▲), DMBA plus teleocidin B-4 (■), teleocidin B-3 alone (△···△), and DMBA alone or each isomer of teleocidin except teleocidin B-3 alone (×). *B*, average number of tumors per mouse in groups as described in *A*.

DISCUSSION

In this work we found that all of the isomers of teleocidins A and B have the same potency to activate protein kinase C and to promote tumor formation. As reported previously (10, 13), all of these isomers have the same specific activities for various biological effects. Therefore, here we discuss the structure-activity relationship of the teleocidin molecule, focusing on the roles of (−)-indolactam-V, the linalyl group in teleocidin A, and the alkylated cyclohexene ring in teleocidin B.

The common structure of teleocidins A and B, (−)-indolactam-V was found to be a possible biosynthetic intermediate of teleocidins A and B (20, 21), and has weaker tumor promoting activity than teleocidins A and B in a two-stage carcinogenesis experiment on mouse skin (7). Thus, a large hydrophobic moiety attached to the (−)-indolactam-V molecule is important for the full activities of teleocidins A and B.

The biological effects of a racemic mixture of *N*-geranyl-(±)-indolactam-V were found to be stronger than those of (−)-indolactam-V but weaker than those of teleocidin A (7). Since a geranyl and a linalyl group have almost the same hydrophobicity, the above results indicate that the linalyl group of teleocidin A should be attached to C-7 of (−)-indolactam-V, not to N-1, for maximum activity.

Results with teleocidin B-1 and des-*O*-methylolivoretin C were interesting with respect to the role of the alkylated cyclohexene ring in the teleocidin B molecule. Teleocidin B-1 had slightly stronger activities than des-*O*-methylolivoretin C for various effects, including tumor promotion (6, 13). These results indicate that the difference in the activities of teleocidin B-1 and des-*O*-methylolivoretin C is probably related to the regioisomeric differences in the cyclohexene ring, suggesting that the cyclohexene ring of teleocidin B requires a vinyl group at C-19 and an isopropyl group at C-25 for higher activities.

A possible precursor of (−)-indolactam-V, *N*-methyl-L-valyl-L-tryptophanol, was found in *Streptoverticillium* (22). Interestingly, *N*-methyl-L-valyl-L-tryptophanol does not bind to phorbol ester receptors or activate protein kinase C *in vitro*.[4] (−)-Indolactam-V might be formed after a nine-membered lactam ring is formed from *N*-methyl-L-valyl-L-tryptophanol.

Recently, on the basis of a ^{1}H-nuclear magnetic resonance study and a force field calculation, Endo *et al.* (23) suggested that teleocidins and olivoretins consist of two major conformers, conformer A (sofa type) and conformer B (twist type), and that the potency of activity might reflect the ratio of conformer A to conformer B. If this is so, the ratio of the two conformers might be similar in the various isomers of teleocidins A and B, because their activities were the same.

In 1983, we reported that the two teleocidin A isomers are (14R)-teleocidin A and (14S)-teleocidin A, according to the numbering system used by Moore's group in 1979 (24), and the four teleocidin B isomers are C-14, C-17-diastereomers according to the numbering system which Hirata's group introduced in 1966 (25). It is required to revise the numbering system for teleocidins A and B from the following reasons: (*a*) the unique common structure, (−)-indolactam-V, was found in *Streptomyces* and culture broth of *Streptoverticillium* (20, 21); (*b*) (−)-indolactam-V is thought to be a possible biosynthetic intermediate of teleocidins A and B (20, 21); (*c*) if so, the carbon atoms of (−)-indolactam-V should be numbered first rather than those of the linalyl group in teleocidin A and the alkylated cyclohexene ring in teleocidin B. The proper numbering system for teleocidins A and B is depicted in Fig. 1. According to this new

[4] Unpublished results.

numbering system, teleocidins A-1 and A-2 are (19R)-teleocidin A and (19S)-teleocidin A, respectively. The four isomers of teleocidin B are C-19, C-25-diastereomers; teleocidin B-1 is (19R, 25S)-teleocidin B, B-2 is (19S, 25R)-teleocidin B, B-3 is (19S, 25S)-teleocidin B, and B-4 is (19R, 25R)-teleocidin B. Tumor promoters of the teleocidin class are very useful for providing information on the structure-activity relationships of tumor promoters.

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