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VISCOMERTIC ANALYSIS OF EFFECTS OF CYTOCHALASANS ON IN VITRO POLYMERIZATION AND DEPOLY-MERIZATION OF MICROTUBULES*

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This paper describes studies which clarify that 19 cytochalasans, including 6 natural cytochalasins, 2 natural aspochalasins, 7 natural chaetoglobosins and 4 their acetates, except for CA do not show any marked inhibitory effects on the association of porcine brain tubulin and also on the dissociation of the microtubule, analyzed by viscosity measurement.

Results of the cytochalasans on the inhibitions of *in vitro* polymerization and

Table I. The Effects of Cytochalasans for the *in Vitro* Microtubule Polymerization and the *in Vitro* Depolymerization of Microtubule determined by Viscometry

Substance	(a—b)/a	(a′—b′)/a′
Cytochalasin A (CA)	0.37 ****a)	0.35 ****a)
Cytochalasin B (CB)	0.05 *	0.00 *
Cytochalasin C (CC)	0.06 *	0.10 *
Cytochalasin D (CD)	−0.03 *	0.00 *
Cytochalasin E (CE)	0.01 *	0.03 *
Cytochalasin H (CH)	−0.08 *	0.05 *
Aspochalasin B (AsB)	0.06 *	0.11 **
Aspochalasin D (AsD)	0.13 **	0.12 **
Chaetoglobosin A (ChA)	0.23 ***	0.16 **
Chaetoglobosin A-Ac (ChA-Ac)	0.19 **	0.06 *
Chaetoglobosin B (ChB)	0.15 **	0.07 *
Chaetoglobosin C (ChC)	−0.03 *	0.01 *
Chaetoglobosin D (ChD)	0.15 **	0.10 **
Chaetoglobosin E (ChE)	−0.05 *	−0.03 *
Chaetoglobosin E-Ac (ChE-Ac)	0.02 *	0.09 *
Chaetoglobosin F (ChF)	0.01 *	0.03 *
Chaetoglobosin F-Ac (ChF-Ac)	0.05 *	0.08 *
Chaetoglobosin J (ChJ)	0.09 *	0.10 **
Chaetoglobosin J-Ac (ChJ-Ac)	0.10 **	0.10 **

a) The values of (a—b)/a and (a′—b′)/a′ were ranked by the nu mber of the asterisk(*) :*; 0.10> (a—b)/a and (a′—b′)/a′, **; 0.20> (a—b)/a and (a′—b′)/a′ ≥0.10,***; 0.30> (a—b)/a and (a′—b′)/a′ 0.20, and ****; 0.40> (a—b)/a and (a′—b′)/a′ ≥0.30.

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depolymerization of microtubules were shown in Table I. The structures of cytochalasans are shown in Fig. 1. The dose-responce curves of the inhibition of the polymerization of microtubule proteins by CA, CC, and ChA were also shown in Fig. 2.

Firstly, the results given in Table I show that no cytochalasans except for CA have activities in the inhibition of microtubule polymerization *in vitro* and of the depolymeriza-

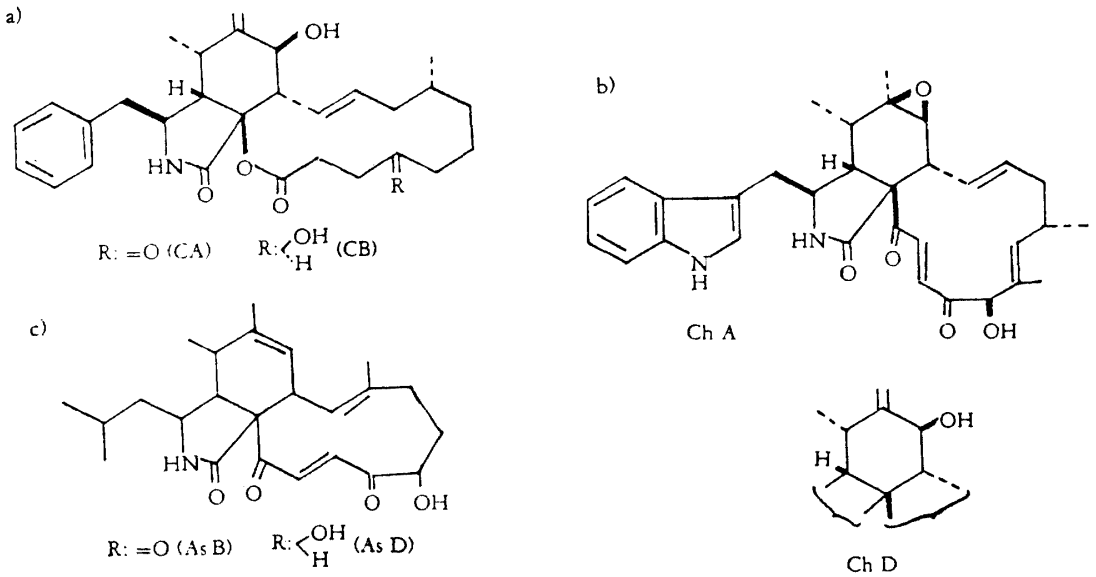

Fig. 1. Structures of Cytochalasans
a) Cytochalasasin A and B, b) Chaetoglobosin A and D,
c) Aspochalasin B and D.

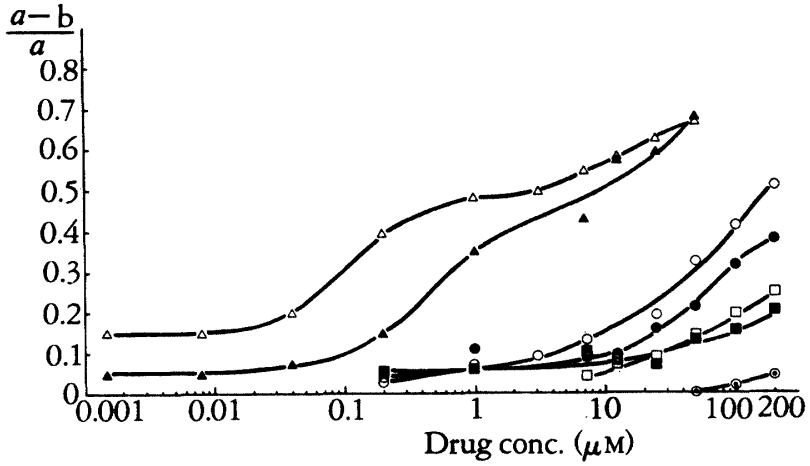

Fig. 2. Dose-responce Curves of the Inhibition of Polymerization of Microtubule Proteins by Vinblastine (△), Colchicine (▲), Griseofulvin (○), Daunomycin (□), Cytochalasin A (■), and C (⊙), and Chaetoglobosin A
Each point is the mean of at least two experiments.

tion of polymerized tubulin (microtubules) *in vitro*. The values of (a—b)/a and (a′—b′)/a′ of CA were 0.37 and 0.35, respectively, and those of ChA follow by 0.23 and 0.16, respectively. All other cytochalasans marked by the asterisk of * or ** have the values of (a—b)/a and (a′—b′)/a′ less than 0.10 or 0.20, respectively, indicating negligible inhibitory activities on the polymerization of porcine microtubules *in vitro*. Fig. 2 represents the dose-responce curves of three cytochalasans : CA, CC, and ChA with those of vinblastine, colchicine and griseofulvin which are known as the sensitive antimitotic drugs, and daunomycin which is also reported as an active component for representative antimitotic drugs, and daunomycin which is also reported as an active component for perturbing the polymerization of tubulin and microtubule assembly. The results obtained in this experiment indicate that, under the conditions in which vinblastine and colchicine inhibit the polymerization of tubulin into microtubules in low concentration, CA showed a slight but distinct effect. However, its activity was lower than that of griseofulvin and higher than those of daunomycin and ChA. The dose-responce curve of CC represents the activities of all other cytochalasans which showed small (a—b)/a values. On the other hand, the micromolar concentrations of drugs which show the value of 0.2 in reference to (a—b)/a were calculated as follows : vinblastine, 0.04 ; colchicine 0.33 ; griseofulvin, 23 ; cytochalasin A, 44 ; daunomycin, 110 ; chaetoglobosin A, 190.

Although data of the present studies were evaluated only on the basis of the results of the viscometric analyses, the results indicate that the *in vitro* traget protein of the cytochalasans is not the tubulins or microtubules. In conclusion, our results could be evaluated in connection with the studies of Yahara et al. which suggested the interaction of cytochalasans with actin.