Title	Disruptive effect of diethylstilbestrol on microtubules
Sub Title	
Author	佐藤, 良博(Sato, Yoshihiro) 村井, 知子(Murai, Tomoko) 円谷, 勝(Tsumuraya, Masaru) 斉藤, 肇(Saito, Hajime) 児玉, 昌彦(Kodama, Masahiko)
Publisher	共立薬科大学
Publication year	1985
Jtitle	共立薬科大学研究年報 (The annual report of the Kyoritsu College of Pharmacy). No.30 (1985.) ,p.105- 106
JaLC DOI	
Abstract	
Notes	抄録
Genre	Technical Report
URL	https://koara.lib.keio.ac.jp/xoonips/modules/xoonips/detail.php?koara_id=AN00062898-00000030-0105

Disruptive Effect of Diethylstilbestrol on Microtubules*

Yoshihiro SATO, Tomoko MURAI, Masaru TUMURAYA**,
Hazime SAITÔ** and Masahiko KODAMA**

佐藤良博，村井知子，円谷　勝**，斎藤　肇**，児玉昌彦**

Diethylstilbestrol (DES) is a synthetic estrogen which is carcinogenic in human and rodents but shows no mutagenicity in *Salmonella*. While DES caused neoplastic transformation of Syrian hamster embryo cells, it did not induce mutation at two conventionally studied loci. Although DES induced mutations in the mouse lymphoma system and sister chromatid exchange in lymphocytes, a unique feature of DES action is the induction of mitotic nondisjunction, aneuploidy or polyploidy. This suggests an analogy with the action of colchicine, an inhibitor of microtubule assembly.

In this report, we present direct evidence that DES is active in inhibiting microtubule assembly *in vitro*. Microtubule protein was extracted from porcine brain in two assembly-disassembly cycles by the method of Shelanski *et al.* with some modifications. Turbidity measurements and viscometry were used to study the *in vitro* assembly and disassembly of microtubules. DES was dissolved in a 1 : 1 mixture of dimethylsulfoxide and N,N-dimethylformamide, and the solution was added at 2% of the total volume to the protein solution before and after assembly. Electron microscopic examination of DES-treated and non-treated samples was done after staining with uranium acetate solution.

The results of viscometry with an Ostwald type viscometer clearly show that DES has an inhibitory effect on microtubule assembly in a concentration-dependent manner up to 200 μM. A comparative extent of disassembly was also observed on addition of DES to assembled microtubules. The data by turbidity measurements are consistent with those obtained by viscometry, except that the increased turbidity at 100 and 200 μM of DES. The reason for this is not clear at present.

Electron microscopic examination showed that at 50 μM of DES microtubule assembly was completely inhibited, although some protofilament-like structures were observed which increased in quantity at 200 μM of DES. On the other hand, disassembly experiments at 50 and 200 μM DES suggested that protofilament-like structure might be formed from microtubules.

In this experiment we also tested the effect of estradiol, which is the most potent naturally occurring estrogen in mammals. However, in spite of the reported inducibility of mitotic nondisjunction in HeLa cells, the results of turbidity and electron microscopy indicated that 200 μm of estradiol has no ability to interact with microtubules or

* 本報告は，*Gann*, **75**, 1046—1048 (1984) に発表

** 国立がんセンター研究所

microtubule protein *in vitro*.

Representative drugs able to disrupt microtubules are colchicine, colcemid, vincristine and vinblastine. Among them, colcemid was recently reported to induce neoplatic transformation in Syrian hamster cells while vincristine was found to be inactive in a C3H mouse cell line. A typical carcinogen that inhibits microtubule assembly is griseofulvin, an antibiotic used to treat dermatophytosis. Potent mitotic poisons may not always be carcinogenic, because carcinogenesis may be initiated by chromosomal nondisjunction without arresting cell growth. Under the present experimental condition, 50 μM of DES, 200 μM of griseofulvin, 10 μM of colchicine and 2 μM of vinblastine produced similar extents of inhibition of microtubule assembly.

On the basis of present *in vitro* evidence together with data from other laboratories, the carcinogenicity of DES may be best explained on the basis of disruption of microtubules, which results in aneuploidy or chromosomal gene unbalance, favoring the develope mnt of tumors.