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Mescaline as a mitotic spindle inhibitor

COLCHICINE and its methyl derivative colcemid not only inhibit microtubule self-assembly[1] but also affect fast transport in nerve[2]. A report that mescaline likewise inhibits the rapid component of axoplasmic transport in nerve[3], led us to investigate the effects of this drug on mitosis, and on purified microtubule protein (tubulin[4]). The structure of mescaline does resemble an abbreviated version of colchicine (Fig. 1). We report here that mescaline can, like colcemid, be used as a mitotic spindle inhibitor and has certain advantages as a cytogenetic reagent.

We first investigated the effect of a range of concentrations of mescaline from just above to just below the limits at which concentrations of colcemid exert an inhibitory influence on mitosis. When human skin fibroblasts are cultured in small dishes, the dividing cells round up so that by mid-metaphase they stand out in marked contrast to the flat cells with a polygonal outline characteristic throughout interphase. If the rounded cells are examined using Nomarski interference optics[5], they can be seen to be in division as one can distinguish the chromosomes in the live cell (Fig. 2). By simply counting the number of rounded cells in a dish, under an ordinary dissecting microscope, one can score any compound for its effect as a mitotic inhibitor.

This first series of experiments (Fig. 3) showed that mescaline was similar to colcemid in its effectiveness. At the higher concentrations, cells treated with colcemid showed some signs of a toxic effect (detachment); those treated with mescaline did not.

A second series of experiments (Fig. 4) designed to study the time course of events up to 24 h after the inoculation of fibroblast cultures with mitotic inhibitors, showed that mescaline is metabolised rather readily, giving a peak of inhibition at 4 h followed by a plateau of moderate inhibition. The first breakdown product of mescaline in human brain is *N*-acetylmescaline[6]. We synthesised this compound,

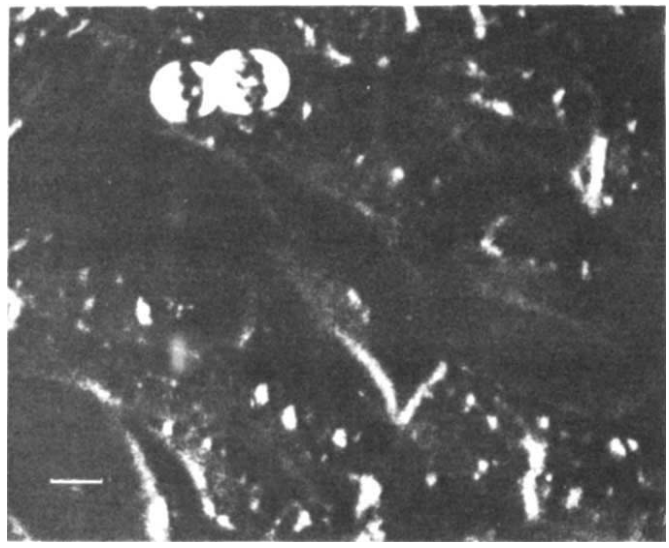

Fig. 2 Nomarski interference image of cells in division. Cells at the top left are in anaphase, with the chromosomes visible on the spindle. The rounded appearance of the dividing cells is in marked contrast with the polygonal interphase cells seen below. The micrograph shows the progress of division past metaphase in the absence of any drug treatment. Bar indicates 20 μm.

and found that it acts in our experimental system as a moderate inhibitor of mitosis. We therefore attribute this plateau effect to the metabolite *N*-acetylmescaline. Colcemid was also metabolised, but more slowly. It is likely that the first step in this process is the demethylation of a methoxy group in ring A of the molecule, as reported for colchicine in mammalian liver[7,8]. Results with 1,4-dichlorobenzene, which is known to be an effective inhibitor of mitosis in plants[9], gave no indication that this agent is metabolised at all.

Our conclusion is that mescaline could be used as a mitotic inhibitor for use in cytogenetic work. Our observations with a variety of human and other mammalian cells show that this drug produces well-spread metaphases suitable for examination by banding techniques (Fig. 5). Mescaline has the advantage that it is 1,000 times less expensive to purchase than is colcemid; it has the disadvantage that its use is controlled by drug legislation.

Our experiments with radioactive mescaline demonstrated that it binds to purified microtubule protein. Like colchicine, it also inhibits the assembly of tubulin subunits to form microtubules. The implications of these findings should be of some general interest. Mescaline is a catecholamine-like neurotransmitter analogue. Its effects on tubulin raise the possibility that neurotransmitters or their

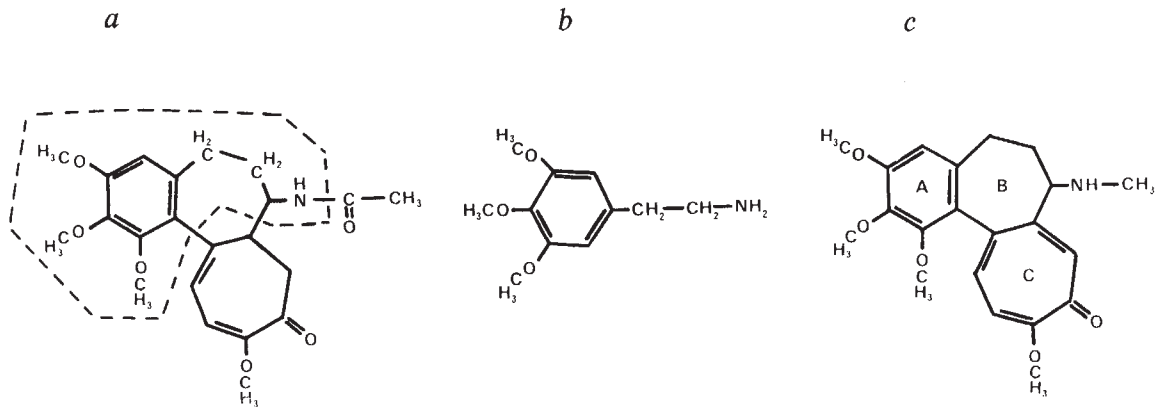

Fig. 1 Structure of spindle inhibitors. *a*, Colchicine; *b*, mescaline; *c*, colcemid. Dotted line indicates the portion of the colchicine molecule to which mescaline would seem to correspond.

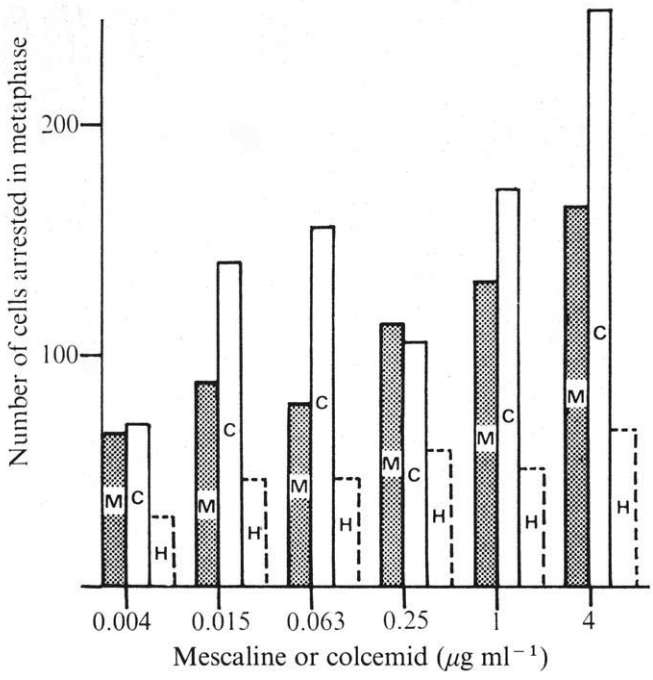

Fig. 3 Comparison of dose responses of human skin fibroblasts to mescaline and colcemid. Cells (2×10^4 per 3-cm Petri dish) were plated out, fed with fresh medium the following day, and exposed to the spindle inhibitors at the dosages indicated. Cell counts were begun 2 h after the start of the treatment and are expressed as the average of a forward and a backward count through the series of dishes. Slight effects of cooling and disturbance are reflected by minor increases in counts in the control dishes. Cells rounding up due to toxic effects at high dosage of colcemid may make some contribution to the count at 4 μg colcemid ml^{-1}. M, Dishes given mescaline in 0.1 ml Hanks' balanced saline; C, dishes given colcemid in 0.1 ml Hanks' balanced saline; H, control dishes given 0.1 ml Hanks' balanced saline.

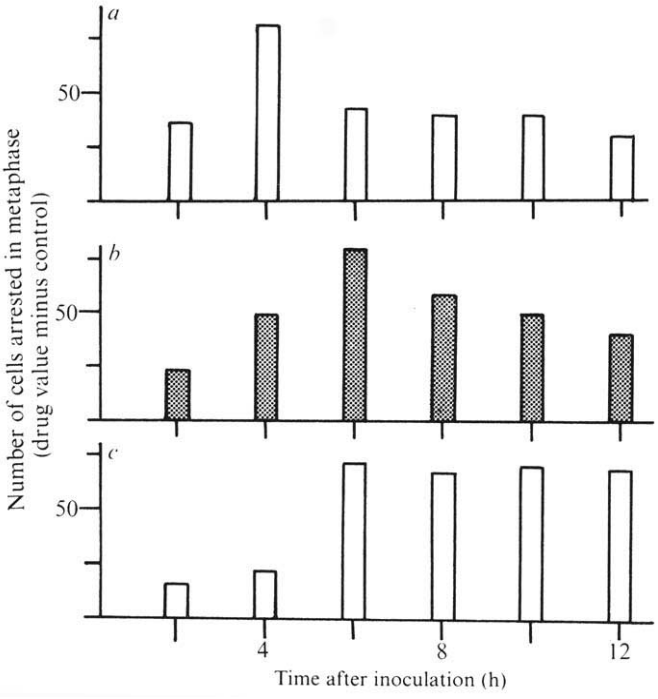

Fig. 4 Time course of effects of spindle inhibitors on human skin fibroblasts. Cells were plated out as in Fig. 3. Counts were made once on each of six sets of dishes at 2 h intervals, each set included a control inoculated with Hank's balanced saline, a dish with colcemid (*a*) at 4 μg ml^{-1}, a dish with mescaline (*b*) at 5 μg ml^{-1}, and a dish inoculated with 0.1 ml saturated solution (*c*) of 1,4-dichlorobenzene in Hanks' balanced saline.

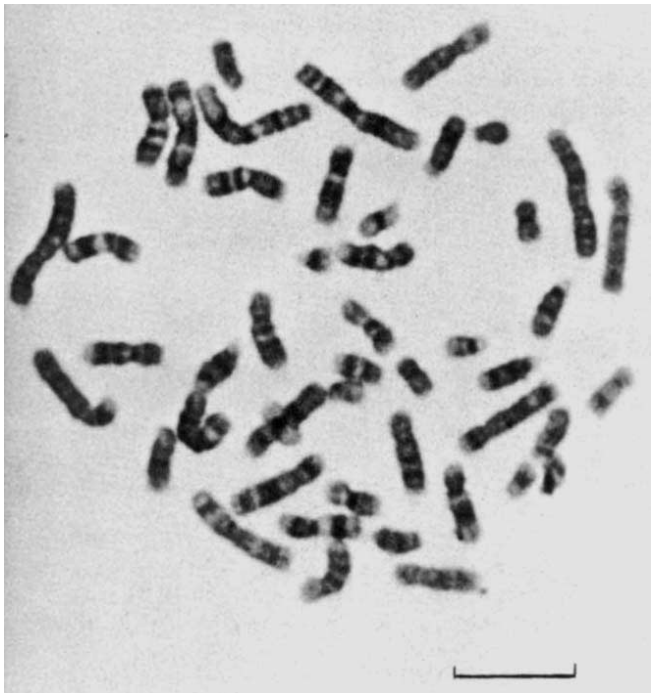

Fig. 5 Metaphase spread from a human leukocyte culture prepared with mescaline as a spindle inhibitor, trypsin-banded and stained with Giemsa. Bar indicates 10 μm.

metabolites may have a separate role additional to their effect at the cell membrane—regulation of the polymerisation state of fibrous proteins within the cell. The biochemical results of this work will be reported separately.

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Antibodies to a cell-surface component coded by human chromosome 21 inhibit action of interferon

Anticellular sera able to block specific cell responses are important in the study of surface receptors. Particularly useful are antibodies against the human cellular antigens coded for by a specific chromosome, which can be prepared by immunising mice with mouse–human somatic cell hybrids containing defined human chromosomes[1]. We have applied this method to the study of the mechanism by which the presence of human chromosome 21 renders such hybrids sensitive to human interferon[2]. Interaction of an interferon with sensitive cells induces intracellular biochemical changes, including the formation of an inhibitor of protein synthesis, making the cell unable