and 68%, respectively, as compared to control values (table). For the same time period, granulation tissue of ear wounds were depressed only 25% below controls. Less depression of nuclear labeling was observed in animals injected with DE at 20 h than at 16 h, and even less in those injected at 24 h. DE did not cause a significant depression of nuclear labeling of maxillary palatal epithelium. LE injections did not depress nuclear labeling of connective tissue or epithelium significantly at any time period.

The reduced proliferation in granulation tissue following DE injection appeared to be discrete and consistent in its timing and apparently specific for connective tissue. This suggests that some factor in the DE may have specifically interrupted or slowed a particular stage in the cell cycle of proliferating connective tissue cells, rather than having caused a generalized cytotoxic effect. Studies with other experimental models have shown that early events following stimulation are important to later DNA synthesis. Inhibition of RNA synthesis 0-4 h after rat hepatectomy depressed DNA synthesis in liver 12-18 h later[6]. And, inhibition of protein synthesis 1-8 h after isoproterenol stimulation of mouse salivary gland resulted in depressed DNA synthesis 20 h later[7]. The G_1 chalone for mammalian epidermis has been shown to depress DNA synthesis in mouse epidermis in vivo maximally between 9 to 20 h after injection[8,9]. This study presents the 1st in vivo evidence (to our knowledge) of a dermal chalone-like substance, present even in neonatal rat dermis, which is capable of suppressing DNA synthesis in proliferating connective tissue. In a lower physiologic concentration, this substance may take part in a negative feedback mechanism to control growth and proliferation of granulation tissue in the healing wound. Further studies are necessary to determine whether this substance is active in embryologic or neoplastic connective tissue growth.

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Inhibition of reserpine-induced PGO waves in the cat by ergot derivatives

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Summary. The number of reserpine-induced PGO waves in the cat is decreased by administration of ergot derivatives. The inhibition is dose-dependent and the various ergot derivatives show differing potencies. The action of the ergot derivatives may result from stimulation of central serotonin receptors. In addition, possible involvement of dopaminergic systems is discussed.

PGO waves, a characteristic phasic electrical activity recorded from the pons, the lateral geniculate bodies and the occipital cortex occur spontaneously just prior to and during paradoxical sleep in the cat, but are also elicited by pharmacological agents such as reserpine which deplete central monoamine stores[1-3]. PGO waves induced by reserpine, the benzoquilizine derivative Ro 4-1284 or p-chlorophenylalanine are inhibited by 5-hydroxytryptophan (5-HTP) or by the lysergic acid derivatives LSD-25, 2-bromo-LSD and methysergide[1, 4-7]. Our investigations indicate that the inhibition of reserpine-induced PGO waves is a common property of several centrally active ergot derivatives.

Experimental. The studies were carried out under local anaesthesia in adult male cats (2.5-3.5 kg) which were immobilized by gallamine and artificially respired. Reserpine, 0.5 mg/kg i.p. was administered 5 h before recording. Under ether anaesthesia the trachea, both femoral veins and a femoral artery were cannulated for artificial respiration, i.v. drug administration and continuous recording of blood pressure, respecitvely. The head of the animal was placed in a stereotactic apparatus. Pressure points and wound edges were infiltrated with novocaine. The electrocorticogram (ECoG) was recorded from screw electrodes over the frontal, sensorimotor and visual cortex. The PGO waves were recorded from bipolar concentric electrodes of 0.5 mm diameter inserted in both lateral geniculate bodies using the Horsley-Clark coordinates A + 7.0, L ± 10.5, H + 3.5 and adjusted to receive optimal electrical signals. PGO waves were simultaneously registered with the ECoG, blood pressure and heart rate on a Grass model 7 polygraph. PGO waves of more than 100 μV amplitude were counted and printed out as cumulative number per 10 min. During the experiment the animals were maintained at 37.5 °C.

Test substances, dissolved either in 0.9% saline or in diluted tartaric acid solution, were administered into the femoral vein. After a pre-drug control period, the drugs were given in increasing doses at intervals of 30 min. Changes in the number of PGO waves counted during each treatment period were compared to the pre-drug control value. At least 3 experiments were performed with each substance.

Investigated ergot derivatives. Dihydroergotoxine methanesulphonate (Hydergine®), dihydroergotamine methanesulphonate, 13-bromo-9,10-dihydroergotamine hydrogentartrate (BZ 23-467), dihydroergostine hydrochloride (DE 145), dihydroergonine hydrochloride (DN 16-457), dihydro-β-ergosine (DQ 27-422), d-lysergic acid diethylamide tartrate (LSD-25), methysergide hydrogenmaleinate, 6-methyl-8β-[4-(p-methoxyphenyl)-1-piperazinyl-methyl]-9-ergolene dimethanesulphonate (PTR 17-402), 6-methyl-8β-[2-pyridylthiomethyl]-ergolene tartrate (CF 25-397), 6-methyl-8α-cyanomethyl-ergoline methanesulphonate (CM 29-712), 2-bromo-α-ergocryptine methanesulphonate (bromocriptine, CB 154).

Results and discussion. The onset of a regular PGO wave pattern in the recordings from the lateral geniculate bodies of the cat, comparable to the stage 2 described by Brooks and Gershon[2], was observed 3-4 h after reserpine administration. At the same time low-voltage fast activity was seen in the ECoG. The frequency of PGO waves (30-50 min^{-1})

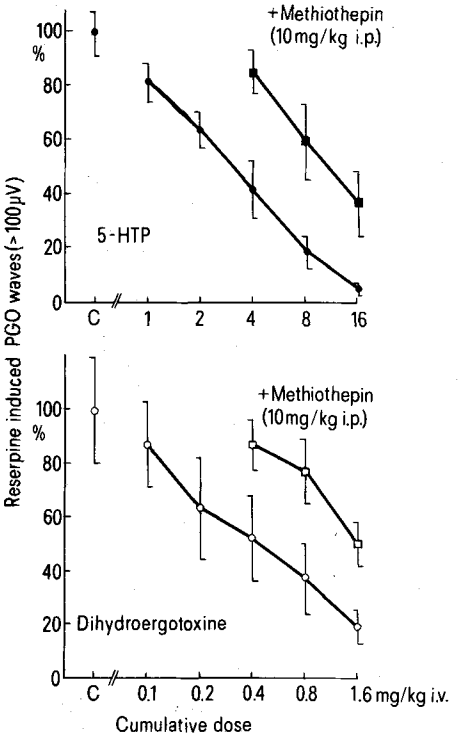
Effects of ergot derivatives on reserpine-induced PGO waves in the cat

Compounds	Number of experiments	Percent inhibition (cumulative dose mg/kg i.v.)					ED_{50} mg/kg i.v.
		(0.1)	(0.2)	(0.4)	(0.8)	(1.6)	
Dihydroergotoxine	5	13	37	48	63	81	0.4
Dihydroergotamine	5	43	53	65	80	91	0.2
BZ 23-467	4	21	32	55	76	94	0.3
Dihydroergonine	4	8	23	45	48	67	0.6
Dihydro-β-ergosine	5	34	67	86	91	94	0.2
		(0.01)	(0.04)	(0.14)	(0.44)	(1.44)	
LSD-25	3	11	57	83	85	99	0.03
Methysergide	3	4	10	26	49	92	0.4
PTR 17-402	4	77	95	96	97	97	<0.01
CF 25-397	3	7	28	80	94	98	0.06
29-712	3	2	1	[10*]	23	77	0.8
		(0.1)	(0.4)	(1.4)	(4.4)	(14.4)	
Dihydroergostine	4	2	13	52	83	99	1.4
Bromocriptine	5	[15*]	[3*]	27	79	91	2.0

[*] Increase in number of PGO waves.

was very stable during the experimental period, and, as was seen in cats bearing chronically implanted electrodes, even 24 or 48 h after reserpine administration similar PGO waves still occur.

All of the ergot compounds tested decreased the frequency of reserpine-induced PGO waves in a dose-dependent manner (table). The reduction took place in a relatively small effective dose range reflected by a steep dose response curve (figure). In each experiment, the decrease was due to a reduction of the number of PGO waves and not to a decrease of wave amplitude. At higher doses, the PGO waves were totally abolished. Among the ergot derivatives investigated, individual potencies in reducing the number



Dose-dependent inhibition of reserpine-induced PGO waves in the cat by 5-hydroxytryptophan (5-HTP) above and dihydroergotoxine below. Methiothepin pretreatment shifts both dose response curves to the right. Each point represents the mean value±SEM of at least 3 experiments.

of PGO waves varied considerably. The ergopeptine derivatives dihydroergotoxine, dihydroergotamine, 13-bromodihydroergotamine, dihydroergostine, dihydroergonine and dihydroergosine with an ED50 between 0.1 and 1.0 mg/kg i.v. were more effective than the serotonin precursor 5-HTP but also considerably less potent than simple lysergic acid derivatives. In order to gain more information about the mechanisms involved in the inhibition of PGO waves by dihydroergotoxine, we pretreated some animals with several receptor blocking agents. in addition to reserpine. Methiothepin (10 mg/kg i.p.)[7,8], administered 30 min after the pre-drug control period, increased the number of reserpine-induced PGO waves by 35% and shifted the dose response curve for the antagonizing effect of both dihydroergotoxine and 5-HTP to the right (figure). Phenoxybenzamine (10 mg/kg i.p.) or pimozide (10 mg/kg i.p. given under the same conditions) had no effect. Like 5-HTP the ergot derivatives changed the low voltage fast activity pattern in the ECoG of the reserpine-treated cats into a pattern of lower frequency and higher amplitudes[9]. In view of the 5-HTP-like effect of several of these compounds on the sleep-wakefulness cycle in the rat[10,11], we suggest that dihydroergotoxine and the other dihydrogenated ergot compounds act as serotonin receptor agonists.

LSD-25 and the ergolene derivatives PTR 17-402 and CF 25-397 decreased the number of reserpine-induced PGO waves at doses around 0.01 mg/kg i.v. LSD-25 was

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found to have a comparable high potency on PCPA- and on benzoquinolizine-induced PGO waves[7]. Like 5-HTP and the dihydrogenated ergots, LSD-25[12] and CF 25-397[13] are able to shorten paradoxical sleep in the rat. Neurochemical and neurophysiological effects consistent with a central tryptamine-like action of LSD-25 and PTR 17-402 have been reported earlier[14-16], whereas data on CF 25-397 will be published[13,17]. In addition, these compounds are known to possess dopamine receptor stimulant properties as well[18-20]. Compared to LSD-25, methysergide was considerably weaker in decreasing reserpine-induced PGO waves. This finding confirms earlier observations.

Bromocriptine had the weakest inhibitory effect on reserpineinduced PGO waves of all ergot derivatives investigated. At lower doses, bromocriptine and CM 29-712 even tended to increase the number of PGO waves. Bromocriptine and CM 29-712 are known as dopamine receptor stimulants without direct actions on serotonin receptors[13].

When surveying our results with ergot derivatives, it appears that the most potent inhibitors of PGO waves - LSD-25, PTR 17-402, CF 25-397 - are potent agonists at central serotonin and dopamine receptor sites. In comparison, dihydrogenated compounds, which were less potent inhibitors of PGO waves, induce, apart from their serotonin-like action, a weaker dopamine receptor stimulation. Finally, the dopamine receptor stimulants CM 29-712 and bromocriptine were the least potent in reducing PGO waves.

Several authors have proposed that PGO wave activity is under the inhibitory control of serotoninergic neurones in the pontine reticular formation[3,21,22]. Our results are in agreement with the hypothesis that ergot derivatives exert their inhibitory action on reserpine-induced PGO waves by stimulating such serotonin receptor sites. However, the differences in potencies observed suggested that, in addition, dopaminergic stimulation might be involved. Indeed, the ability of ergot derivatives to counteract reserpine-induced akinesia has been ascribed to stimulation of striatal dopamine receptors[13,23]. Furthermore, an inhibitory pathway descending from the striate nucleus to the pontine region[24] has been described which might be involved in the inhibitory effect of bromocriptine on morphineinduced analgesia[9,13,25]. Therefore it is suggested that part of the inhibition by ergot derivatives of reserpine-induced PGO waves is brought by stimulation of striatal dopamine receptors.

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Cytostatic activity of organic compounds and their average quasi-valence number

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Summary. It is found that the average quasi-valence numbers of alkylating cytostatics lie in the region of potential carcinogens, while the average quasi-valence numbers of antimetabolites predominantly cover the region of noncarcinogens. Implications of this finding on the design of new drugs are discussed.

Material and methods. The potential of electron-ion interaction[1] has been calculated for a large number of organic compounds and related to their biological effects in mammals[2]. On the basis of this work, a simple theoretical criterion of chemical carcinogenicity has been developed[3]. It is shown that the average quasi-valence number (the ratio of the sum of all atomic valence electrons[4] and the number of atoms in the molecule) for potential carcinogens is lower than 3.20, while the average quasi-valence numbers of noncarcinogens exceed the borderline value of 3.20.

Further analysis[5] has disclosed the correlation between the types of carcinoma and the average quasi-valence number in case of 110 carcinogenic substances thorougly evaluated by Lyon experts[6]. Organic compounds, depending on their average quasi-valence numbers, can cause different types of carcinoma in mammals. This reveals specific biological activity of chemical compounds in vivo.

On the basis of the above findings, one might expect that different drugs used for curing the same illness(es) should have similar or rather close average quasi-valence numbers. The preliminary data on antibiotics, hormones, psychopharmaceuticals and some other classes of organic substances have shown that this is indeed the case.

Results and discussion. Results of the average quasi-valence number calculation in the case of 105 alkylating organic compounds investigated by A. Golding and H.B. Wood, Jr, of the USA National Cancer Institute[7], are presented in the figure.

Most alkylating substances (95%), characterized by average quasi-valence numbers lower than 3.20, cover the region of potential carcinogens. Only in 5 cases do the corresponding average quasi-valence numbers exceed the borderline of noncarcinogenicity (3.20).

All alkylating substances (mainly belonging to different nitrogen mustards) producing 50% or higher increase in the life span in systemic leukemia L1210, have average quasi-valence numbers below the value of 3.20. Similar results are obtained for alkylating agents-antitumour drugs used in clinical practice. A survey of such agents[8] is given in table 1. Only one drug out of 24 has a higher average quasi-