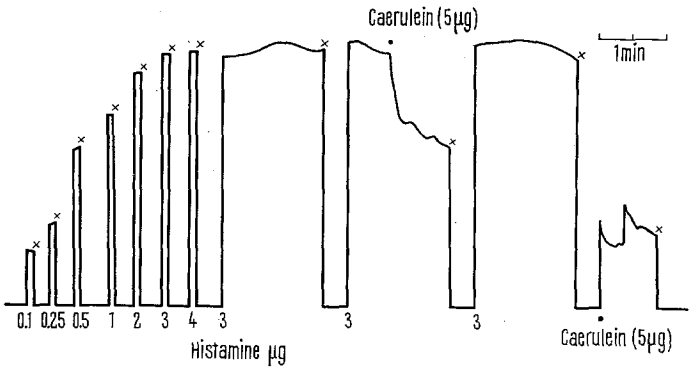

Guinea-pig ileum preparation in a 10 ml bath containing Krebs solution. ×, washing.

100–500 times as high as those of caerulein, failed to produce any inhibitory effect, whereas cholecystokinin-pancreozymin (CCK) behaved exactly as caerulein. Therefore we suggest that this phenomenon may be considered as a simple and rapid method of discrimination between gastrin-like and CCK-like activities. As repeatedly stated[4], caerulein though possessing structural similarities with gastrin and CCK as well, is much more like CCK than gastrin as to pharmacological activities.

We are carrying out further investigations in order to elucidate the mode of action of this peculiar effect of caerulein and of some caerulein analogues[5].

Riassunto. La caeruleina provoca sull'ileo di cavia isolato una inibizione dello spasmo sostenuto da dosi massimali di istamina. Questo effetto inibitorio sembra connesso con le proprietà colecisto-chinino simili del peptide più che con quelle gastrino simili.

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Brain Damage in Rats Following Pentylenetetrazole and High Pressure Oxygen

Exposure of rats and mice to high pressures of oxygen (HPO) results in convulsions, haemorrhagic consolidation of the lungs and death. A proportion of animals given shorter exposures to HPO and which survive also display neurological damage, ranging in severity from hyperexcitability and incoordination of movements to severe spastic paralysis[1].

Barbiturate anaesthesia prevents convulsions and lung damage from HPO and increases survival, but also increases the incidence of brain damage[2,3]. Chemical convulsants such as pentylenetetrazole (PTZ) cause lung damage in rats identical to that caused by HPO[4,5].

The studies of BEAN et al.[4] have provided strong evidence that oedemogenic lung lesions caused by convulsive agents in general (including HPO and PTZ) are primarily due to the effect of the agent on autonomic centres in the central nervous system and central stimulation of neuroendocrinological pathways, particularly those associated with the sympathetic system. This hypothesis is supported by: a) adrenergic antagonists and blocking agents protect against lung damage produced by both HPO and chemical convulsants, b) oedemogenic lung lesions are readily produced by large i.v. doses of adrenaline[6] and by related adrenergic compounds, particularly methoxamine[7], c) similar pulmonary lesions can be produced in rats by focal damage to the preoptic area of the rostral hypothalamus[8], d) the interruption of certain pathways for autonomic outflow protects against lung damage in rats exposed to convulsants[4], and e) discrete lesions in the CNS, particularly in the hypothalamic regions of the brain stem, have been demonstrated histologically in rats exposed to HPO[9–11].

In view of the similar effects of PTZ and HPO in causing convulsions and lung damage, studies were undertaken to determine. 1. if PTZ also produced paralysis in unanaesthetized and anaesthetized rats, and 2. the effect of combined treatments of rats with PTZ and HPO on the incidence of paralysis.

Six- to seven-week-old female Caworth farm rats (from specific pathogen free derived colony) were used. Unanaesthetized rats were given 1.0–2.8 ml PTZ/kg body weight i.p. All convulsed severely within 60 sec, and died within 4–30 min, and all rats showed severe lung damage at necropsy. In 30 rats which were anaesthetized with pentobarbital Na (38 mg/kg body weight i.p.) prior to

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PTZ (1.0–2.0 ml/kg) convulsions, apart from minor twitching, did not occur, all rats recovered consciousness, and were alive 24 h later without evidence of spastic paralysis. Furthermore, rats from these groups showed no evidence of lung damage when killed 1–24 h after treatment with PTZ. Thus in 13 unanaesthetized rats given PTZ (1.0 ml/kg) all died with damaged lungs which weighed 13.5 + 1.6 mg/kg body weight at necropsy, compared with 6.0 ± 0.4 mg/kg (10 untreated control rats), with 6.5 ± 0.7 mg/kg (9 anaesthetized rats given 2 ml/kg PTZ and killed 1 h later) and with 6.9 ± 0.5 mg/kg (6 anaesthetized rats given 2 ml/kg PTZ and killed 24 h later).

Thus, whilst anaesthesia prevents convulsions and lung damage in rats given PTZ or exposed to HPO and the rats survive the treatments, PTZ differs from HPO in that it did not cause paralytic brain damage in barbiturate 'protected' rats. Also, paralysis was not produced in unanaesthetized rats given lower doses of PTZ which caused less severe convulsions and lung damage and allowed a proportion of rats to survive the next day. An attempt to produce paralysis with higher doses of PTZ (2 × 2.8 ml/kg) given to anaesthetized rats resulted in death with lung damage without the rats having regained consciousness.

Incidence and severity of paralysis[a] in rats exposed to high pressure oxygen (HPO) at 5 ATA (60 p.s.i. gauge pressure) for varying times, and the effect of pre- and post-pressurization treatment with pentylenetetrazole (PTZ)

Exposure times	Dose of PTZ (ml/kg)[b] given immediately before or after HPO	Deaths < 24 h after treatment (%)	Rats with paralysis (Grade 2–5 severity) (%)	Index of severity of paralysis[a]
15 min	Nil	0/11 (0)	0/11 (0)	0.55 ± 0.16
	1.4 before	0/18 (0)	0/18 (0) (n.s.)	0.00 ($p < 0.05$)
	2.8 before	1/6 (17)	1/5 (20) (n.s.)	1.40 ± 0.68 (n.s.)
	1.4 after	0/12 (0)	7/12 (58) ($p < 0.05$)	1.75 ± 0.37 ($p < 0.01$)
	2.8 after	0/6 (0)	4/6 (67) ($p < 0.05$)	1.70 ± 0.42 ($p < 0.01$)
20 min	Nil	3/18 (17)	12/15 (80)	2.80 ± 0.34
	1.4 before	0/18 (0)	2/18 (11) ($p < 0.01$)	0.56 ± 0.20 ($p < 0.001$)
	2.8 before	0/6 (0)	1/6 (17) (n.s.)	0.50 ± 0.34 ($p < 0.01$)
	1.4 after	1/12 (8)	9/11 (82) (n.s.)	3.36 ± 0.54 ($p < 0.05$)
	2.8 after	2/6 (33)	4/4 (100) (n.s.)	3.50 ± 0.50 (n.s.)
30 min	Nil	1/23 (4)	15/22 (68)	3.05 ± 0.42
	1.4 before	0/24 (0)	3/24 (12) ($p < 0.01$)	0.54 ± 0.19 ($p < 0.001$)
	2.8 before	1/6 (17)	4/5 (80) (n.s.)	2.80 ± 0.66 (n.s.)
	1.4 after	1/18 (6)	11/17 (65) (n.s.)	2.82 ± 0.42 (n.s.)
	2.8 after	0/6 (0)	6/6 (100) (n.s.)	3.50 ± 0.62 (n.s.)

All rats anaesthetized with pentobarbital sodium i.p. before exposures. [a] Scored (Grades 1–5) according to severity[3]. [b] 10% solution (w/v) of PTZ (Leptazol BPC) used for i.p. injections.

To determine whether PTZ altered the incidence and severity of paralysis produced by HPO in anaesthetized rats, 190 rats were anaesthetized with pentobarbital Na. All rats were exposed to HPO (5 ATA for 15–30 min) as described previously[3]; 78 of these rats received 1.4–2.8 ml PTZ/kg immediately *before pressurization* in oxygen, 60 rats received PTZ immediately *after decompression* in oxygen, and the remaining 52 rats were not treated with PTZ. Paralysis was scored 24 h later. The results obtained (Table) suggest that at certain levels of PTZ dosage and of exposure to HPO, PTZ reduces paralytic brain damage produced by HPO provided PTZ is given before exposure to HPO, whilst PTZ tended to increase brain damage if administered after HPO.

The explanation for these effects of PTZ on brain damage due to HPO is not clear. If PTZ caused cerebral vasoconstriction[12], which would reduce the rise in cerebral pO_2 caused by HPO, the results obtained would be largely explained. Other studies in dogs[13] and rats[14] suggest, however, that PTZ increases cerebral blood flow, and the oxygen consumption, acidity and pCO_2 of cerebral tissues, but this does not preclude the possibility that PTZ causes focal reductions in cerebral blood flow in certain parts of the brain (hypothalamus and brain stem)[9–11] which show damage in rats with paralysis after exposure to oxygen. This would also help to explain why PTZ by itself failed to cause paralysis in anaesthetized and unanaesthetized rats, but could enhance paralysis from damage produced in these regions by HPO when administered after exposure to HPO. On the other hand the antagonistic actions of PTZ to barbiturates need to be taken into account. A similar reduction in paralysis produced by HPO in barbiturate-treated rats resulted when the antibarbiturate drug ββ-methylethyl glutaramide was administered together with the barbiturate[3].

It is concluded that the classical effects of HPO in producing convulsions ('Paul Bert Effect') and lung damage ('Lorraine Smith Effect') which terminates in death of the animal are also produced by chemical convulsants such as PTZ and that lung damage produced by HPO is primarily due to its neurological effects[4]. However, paralytic brain damage represents a more specific neurotoxic action of oxygen. It is a toxic effect which a chemical convulsant (PTZ) not only failed to produce to a significant degree, but was decreased by pretreatment of HPO exposed animals with PTZ.

Résumé. La pentylénetétrazole (PTZ) et l'oxygène à haute pression (OHP) ont des propriétés en commun; tous deux causent des convulsions et du dommage aux poumons chez les rats. Elles diffèrent en ce que l'OHP – mais non pas la PTZ – produit au cerveau une paralysie spastique. On a trouvé que la PTZ, donnée avant et non pas après l'exposition des rats à l'OHP, réduit la paralysie du cerveau.

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