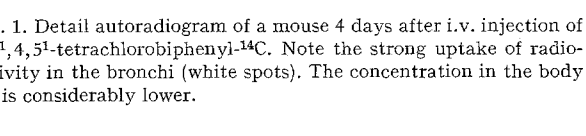

Fig. 1. Detail autoradiogram of a mouse 4 days after i.v. injection of 2, 2^1, 4, 5^1-tetrachlorobiphenyl-^{14}C. Note the strong uptake of radioactivity in the bronchi (white spots). The concentration in the body fat is considerably lower.

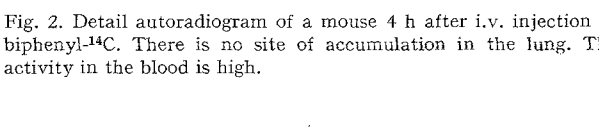

Fig. 2. Detail autoradiogram of a mouse 4 h after i.v. injection of biphenyl-^{14}C. There is no site of accumulation in the lung. The activity in the blood is high.

time, a definite localization of label was observed also in the fetal bronchi. In contrast to the 2, 2^1, 4, 5^1-tetrachlorobiphenyl-^{14}C, the unsubstituted biphenyl-^{14}C was distributed very evenly throughout the lung (Figure 2), with no tendency towards concentration in specific structures.

The present results show that the ability to accumulate in the bronchi is not primarily bound to the biphenyl nucleus itself, but appears at chlorination of the molecule. They also further support the opinion that specific structural requirements exist – the fullfillment of which indicates substances with a high affinity for the bronchial tissue. Thus it was possible to predict the pulmonary behavior of 2, 2^1, 4, 5^1-tetrachlorobiphenyl in mice. The Table classifies some PCBs according to their pulmonary distribution pictures, and illustrates the differences in the chlorine positions. It is, however, possible that investigations into the mechanism of accumulation will give further information about the critical features in the substitution pattern of the biphenyls.

An important question in this respect is whether the radioactivity in the bronchial mucosa represents metabolized or unchanged PCB, or both. It has been demonstrated that intermediates to halogenated benzenes (e.g. chlorobenzene) covalently bind to the bronchial epithelium, where they cause tissue necrosis[15]. A similar mechanism of binding may be involved for the PCBs. Another possibility is that the bronchial concentration of radioactivity reflects a specific excretion pathway for certain PCB-structures or their metabolites in the lung.

The biological significance of these observations is at present unknown. Few investigations have been reported concerning chronic effects of structurally defined PCBs in laboratory animals, and pulmonary lesions have so far not been observed. It was recently shown that the uptake of 2, 2^1, 4, 4^1, 5, 5^1-hexachlorobiphenyl-^{14}C in mice bronchi was almost completely blocked when the mice were pretreated with a large dose of the unlabelled isomer[3]. This may indicate that a possible adverse effect will not follow a simple dose-response relationship, and therefore not easily be provoked in short term high dose experiments. Obviously more attention should be paid to the late effects of defined PCBs in the different species. It is notable that 2, 2^1, 4, 4^1, 5, 5^1-hexachlorobiphenyl is a major PCB-component in human fat as well as in the fat of fisheating birds and seals[16].

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Thermoregulatory Effects of Histamine

B. COX, M. D. GREEN and P. LOMAX[1]

Department of Pharmacology, School of Medicine and The Brain Research Institute, University of California, Los Angeles (California 90024, USA), 18 November 1975.

In recent years there has been considerable neurochemical evidence, including regional distribution, cellular localization and the presence of synthetic enzymes, to implicate histamine as a putative central neurotransmitter. Central thermoregulatory mechanisms constitute one neuronal system on which a neurophysiological response to histamine can be demonstrated[2]. Thus, in the rat injection of histamine directly into the rostral hypothalamus causes a fall in body temperature which can be prevented by systemic administration of histamine H_1-

Table I. The effect of McN-A-1293 injected into the lateral ventricle on histidine induced hypothermia in animals pretreated with Ro4-4602 (30 mg.kg^{-1} i.p.) 30 min earlier

Drug (dose)	No. of animals	Mean fall in body temperature (°C ± SEM)
0.9% NaCl (1 µl i.vent.) + 0.9% NaCl (1 ml.kg^{-1} i.p.)	8	0.2 ± 0.13
Histidine (800 mg.kg^{-1} i.p.)	8	1.3 ± 0.16[a]
McN-A-1293 (40 µg i.vent.) + 0.9% NaCl (1 ml.kg^{-1} i.p.)	6	0.2 ± 0.09
McN-A-1293 (40 µg i.vent.) + histidine (800 mg.kg^{-1} i.p.)	6	0.5 ± 0.20[b]

[a] Significantly different from saline control. [b] Significantly different from histidine alone, $p < 0.05$ (Mann Whitney U-test).

Table II. The effect of McN-A-1293 injected into the third ventricle on heat exposure after histidine loading of rats pretreated with Ro4-4602 (30 mg.kg^{-1} i.p.)

Drug (dose)	No. of animals	Time of exposure to heat lamp (min ± SEM)
0.9% NaCl (1 ml.kg^{-1} i.p.)	6	5.8 ± 0.96
Histidine (800 mg.kg^{-1} i.p.)	6	10.5 ± 0.84[a]
McN-A-1293 (40 µg i.vent.) + 0.9% NaCl (1 ml.kg^{-1} i.p.)	5	5.7 ± 0.49
McN-A-1293 (40 µg i.vent.) + histidine (800 mg.kg^{-1} i.p.)	6	6.5 ± 0.68[b]

[a] Significantly different from saline control. [b] Significantly different from histidine alone, $p < 0.01$ (Mann Whitney U-test).

receptor antagonists such as pyrilamine[3]. Histamine must be injected intracranially in such studies since it does not readily penetrate the blood-brain barrier.

An alternative approach to the study of the central effects of histamine has been to increase brain levels by systemic injection of high doses of its immediate precursor histidine. Whole brain histamine levels can be increased 50–200% by this manoeuvre[4,5]. Such histidine loading will lower core temperature in the rat and the response can be blocked by prior intraventricular injection of histamine H_2-receptor antagonists, such as burimamide[6].

These experimental data indicate that there are both H_1- and H_2-receptors for histamine in the central thermoregulatory pathways. Studies in the rat[7] and the cat[8] have suggested that the H_1-receptors are situated in the rostral hypothalamic thermoregulatory centers and their activation by intracranial injection of histamine results in a lowering of the set level of the thermostat. On the other hand, H_2-receptor stimulation activates heat loss mechanisms (peripheral vasodilation and increased heat loss) in the rat[7,9].

That the thermoregulatory effect of histidine loading is indeed the result of the induced rise in brain histamine, and not due to other nonspecific actions of the precursor, is indicated by the study of GREEN et al.[10]. This problem has now been pursued one step further using an inhibitor of histidine decarboxylase, which is the enzyme involved in the conversion of histidine to histamine in the brain[11]. Taylor et al.[12] have reported that 4-imidazolyl-3-amino-2-butanone (McN-A-1293), although somewhat less potent than other L-aromatic amino-acid decarboxylase inhibitors, is more specific for histidine decarboxylase.

Groups of rats (female Sprague-Dawley weighing 180–200 g) were prepared with chronically implanted (at least 10 d) guides allowing injections to be made into the left lateral ventricle. 8 of these animals were tested, in random order on alternate days, with 0.9% NaCl (1 µl i. vent.), L-histidine HCl (800 mg. kg^{-1} i.p.) and McN-A-1293 (40 µg i. vent.) (supplied by McNeil Laboratories) 30 min after pretreatment with Ro4-4602 (30 mg. kg^{-1} i.p.) (Ro4-4602 is an inhibitor of histidine decarboxylase which does not penetrate the blood-brain barrier and so minimizes the conversion of histidine to histamine outside the central nervous system). As seen in Table I histidine loading resulted in a significant fall in body temperature. Intraventricular injection of McN-A-1293 had no *significant* effect on core temperature by itself but prevented the fall after histidine.

Thermoregulatory behavior was neasured using the method described in detail elsewhere[13]. Briefly, the animals were exposed to a heat lamp under standardized conditions and the time before the animal moved away was recorded. A group of 6 animals with intracerebral injection guides was tested over a 10 d period: Ro4-4602 was injected at 08.00 h; at 08.30 h one of the drug combinations listed in Table II was administered; 60 min later behavioral testing was started. Histidine alone significantly increased the period of heat exposure, compared to NaCl controls. McN-A-1293 injected into the ventricles did not effect exposure time in NaCl controls and abolished the increased heat exposure induced by histidine loading (Table II). The significance of the increased heat exposure after histidine can be summarized as follows: If a compound lowers body temperature by activating heat loss mechanisms, whilst leaving the thermoregulatory centers intact, behavioral mechanisms will reflexly come into play so as to counteract the falling temperature. Thus, the animal remains under the heat lamp long enough for the body temperature to return to the set level – as was confirmed by body temperature measurements taken immediately prior to, and following, heat exposure. On

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the other hand, if the drug acts to lower the set temperature the animal will avoid the heat lamp so as to 'allow' the body temperature to fall to the new level[13].

Although facilities for the measurement of regional brain histamine turnover were not available at the time of the present experiments, since McN-A-1293 has no effect alone but reduces both the fall in body temperature and the associated thermoregulatory behavior after histidine loading, it is reasonable to ascribe these phenomena to the only known effect of the compound – inhibition of histidine decarboxylase. Thus, the data confirm previous impressions[7] that the hypothermic effects of histidine loading is the result of increased brain histaminergic activity in the efferent heat loss pathways.

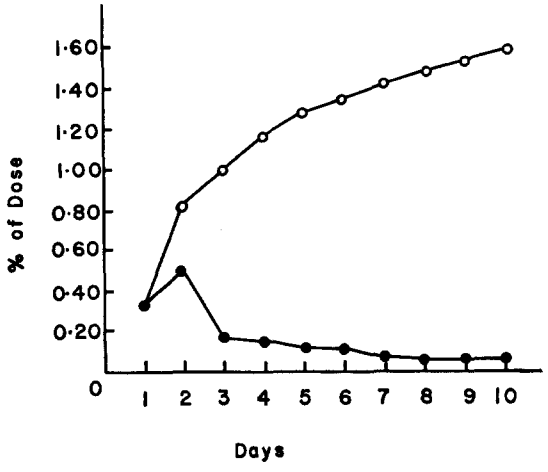
DDT: The Degradation of Ring-Labeled ^{14}C-DDT to $^{14}CO_2$ in the Rat

M. B. ABOU-DONIA[1] and D. B. MENZEL

Departments of Physiology and Pharmacology and of Medicine, Duke University Medical Center, Durham (North Carolina 27710, USA), 20 October 1975.

Summary. Ring fission of *p,p'*-DDT was studied in the rat following a single oral dose of 0.74 mg/kg (1.04 μCi) of uniformly ring-labeled ^{14}C-DDT. Expired air was passed through a solution of ethanolamine-ethylene glycol monomethyl ether (1:2) to trap $^{14}CO_2$. A total of 1.6% of the radioactivity administered was recovered in the expired air collected continually for 10 days, indicating that while degradation of the phenyl moiety is not a major route pf *p,p'*-DDT metabolism in the rat, it is equal to the urinary excretion. Nevertheless, these results represent the most radical change accomplished in vivo of a residual insecticide yet reported in mammals.

Increased attention has been drawn to the ecological significance of *p,p'*-DDT[2]. This growing concern is generally attributed to the stability and the subsequent persistence of DDT-type compounds especially DDE in the environment[3,4]. Because of the accumulation of *p,p'*-DDT and its metabolites in the animals, the pathways of excretion are important to the assessment of hazard since excretion is a major means of protection against accumulation and toxicity. It is surprizing, however, that despite the very high rates of usage of *p,p'*-DDT over the past 45 years, knowledge of its degradation pathways in biological and nonbiological systems is incomplete. Metabolic studies of *p,p'*-DDT have been concerned almost entirely with the loss of only 1 out of the 14 carbon atoms of the molecule[5]. This is exemplified by studies showing the conversion of *p,p'*-DDT to DBP in rats[6] and bacteria[7] and to DBP, DBH and DDM in chicks[8]. The cleavage of one of the phenyl rings of DDM to yield *p*-chlorophenyl acetate by *Hydrogenomonas* has been established[9,10]. The purpose of the present study is to determine whether the rat is also capable of degrading the phenyl ring of the *p,p'*-DDT.



Daily rate (●) and accumulated (○) $^{14}CO_2$ in the expired air from rats following a single oral dose of ring-labeled ^{14}C-DDT.

Materials and methods. White male rats (Cheek & Jones, Houston, Texas), weighing approximately 250 g, were placed in individual Cary animal cages (Glass Instruments, Inc., Pasadena, California). The Cary animal cage, designed especially for studies of expired $^{14}CO_2$ contained coarse and fine mesh screens to separate fecal material from urine which was collected in a separate flask. The expired air was drawn out through this flask by use of a water aspirator. The animals were allowed to adjust to their environment for 1 week subsequently, each of 12 rats was fed a single 0.74 mg/kg dose (1.04 μCi) of ^{14}C-DDT (specific activity of 5 mCi/mmole, New England Nuclear) in a gelatin capsule. ^{14}C-DDT had radiochemical purity of more than 99.5%. 4 similar rats were not fed *p,p'*-DDT and served as controls. The animals were returned to their cages and given free access to food and water. $^{14}CO_2$ was trapped in a solution of ethanolamine-ethylene glycol monomethyl ether (1:2 v/v). ^{14}C-radioactivity was measured by a Beckman model

[1] Acknowledgment. We acknowledge the secretarial work of Ms. ELAINE SMOLKO. This study was supported by NIH fellowship No. 1 F22 ES01723-01 and No. HL16264.

[2] Abbreviations: 1,1,1-trichloro-2,2-*bis*(*p*-chlorophenyl)ethane,(*p,p'*-DDT); 1,1-dichloro-2,2-*bis*(*p*-chlorophenyl)ethane, (*p,p'*-DDD); 1,1-dichloro-2,2-*bis*(*p*-chlorophenyl)ethylene, (DDE); 1-chloro-2,2-*bis*(*p*-chlorophenyl)ethylene, (DDMU); 1-chloro-2,2-*bis*(*p*-chlorophenyl)ethane, (DDMS); unsym-*bis*(*p*-chlorophenyl)-ethylene, (DDNU); 2,2-*bis*(*p*-chlorophenyl)ethanol, (DDOH); *bis*(*p*-chlorophenyl)acetic acid, (DDA); *bis*(*p*-chlorophenyl)methane, (DDM); 4,4'-dichlorobenzophenone, (DBP); and *bis*(*p*-chlorophenyl)methanol, (DBH).

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