Increased concentration of homovanillic acid in the brains of infant rabbits after administration of haloperidol to their nursing mothers

Recently these laboratories have demonstrated that oral treatment of nursing rabbit (Lundborg, 1972) or rat (Ahlenius, Brown & others, 1973) mothers during the first postnatal week with the catecholamine receptor blocking agents haloperidol (rabbits) and penfluoridol (rats) results in permanent behavioural and biochemical abnormalities in their offspring. It was suggested that the first postnatal week in these species could be considered "vulnerable" in respect to the brain dopamine neurons, and that the drugs had penetrated into the breast milk in amounts sufficient to cause pharmacological effects.

Direct evidence for the penetration of neuroleptic drugs into the breast milk to our knowledge has not been presented, even if the high lipid solubility and rapid penetration of the drugs into the brain to support such a possibility. Therefore, to prove the presence of such drugs in the breast milk, we have examined brains from the nursing infants of drug-treated mothers for their content of homovanillic acid (HVA) the major metabolite of dopamine. It has been suggested that blockade of the brain dopamine receptors by e.g. haloperidol results in an increased release of transmitter from the neurons with a compensatory stimulation of the catecholamine synthesis. Such an increase in release of dopamine results in an increase in the levels of the phenolic acids in the brain (Andén, Roos & Werdinius, 1964; Roos, 1965). From previous studies (Kellogg, Lundborg & Roos, 1972) we know that a small dose of haloperidol, given subcutaneously to infant rabbits, causes a significant increase in their brain HVA content. Hence, an increase in brain HVA levels of nursing rabbit infants in response to haloperidol administration to their mothers could be used as a test for the uptake of the drug into the mother's milk and oral intake by the infants.

Seventeen albino female rabbits of the same strain and from the same source were kept in the department for at least 14 days before mating. The pregnant animals were kept in cages in the same animal room. The time of birth could be determined with an accuracy of 3–4 h. The animals had free access to a standard rodent diet.

At parturition, 12 mothers were randomly chosen as experimental animals and the other five as controls. The infants and their nursing mothers were killed on the fourth day after delivery, having received the following treatment. One experimental group was given haloperidol, 1 mg kg^{-1} (dissolved in 2–3 drops of glacial acetic acid plus 5 ml of 5% glucose), in the daily supply (500–600 ml) of drinking water during the last 24 h before death. The control animals were similarly given acetic acid and glucose, but not haloperidol. Another experimental group was given haloperidol (1 mg kg^{-1} day^{-1}) in the drinking water during the 72 h before death.

Immediately after death the brains were removed and chilled with ice. One adult brain or 2–3 pooled infant brains were used for each determination of HVA according to Korff, Roos & Werdinius (1971). The increase in HVA content of the mother's brain was used as a test that the mother had taken the haloperidol-containing water.

When haloperidol (1 mg kg^{-1}) had been administered *via* the drinking water over 24 h, the brain HVA content of the nursing mothers increased from about 0·45 to about 0·87 $\mu g\ g^{-1}$ (Table 1). A significant increase from about 0·13 to about 0·17 $\mu g\ g^{-1}$ was simultaneously observed in the brains of their infants. After treatment of the nursing mothers for 72 h before death, the brain concentrations of HVA were similarly increased in the brains of both mother and infant. No significant difference ($P > 0·1$)

Table 1. *Homovanillic acid (HVA) concentrations in the brains of 4 day old rabbits and their nursing mothers after administration of haloperidol* (1mg kg^{-1} day^{-1}) *or glucose to the mothers in the drinking water for various periods of time.* Values given are means ± s.e.m. and numbers in parentheses indicate number of experiments. * denotes a significant difference between control and treated groups at $P < 0{\cdot}025$, and ** $P < 0{\cdot}001$. † denotes values from Kellogg & others (1972) which have been included for comparative purposes.

Treatment	Route of administration	Age	Duration of treatment	Brain HVA concentration $\mu g\ g^{-1}$
Haloperidol 1 mg kg^{-1} day^{-1}	Oral to nursing mother	Infants	3 days	0·163 ± 0·006 (15)
Haloperidol 1 mg kg^{-1} day^{-1}	Oral to nursing mother	Infants	1 day	0·174 ± 0·011 (11) *
Glucose	Oral to nursing mother	Infants	1 day	0·134 ± 0·009 (7)
Haloperidol 1 mg kg^{-1} day^{-1}	Oral	Adults	3 days	0·724 ± 0·064 (6)
Haloperidol 1 mg kg^{-1} day^{-1}	Oral	Adults	1 day	0·867 ± 0·065 (6) **
Glucose	Oral	Adults	1 day	0·445 ± 0·036 (5)
Haloperidol† 0·2 mg kg^{-1}	s.c.	Infants	4 h	0·276 ± 0·017 (6) *
Glucose†	s.c.	Infants	4 h	0·176 ± 0·032 (6)
Haloperidol† 0·2 mg kg^{-1}	s.c.	Adults	4 h	1·058 ± 0·042 (11) **
Glucose†	s.c.	Adults	4 h	0·465 ± 0·032 (7)

was, however, observed between those animals treated for 72 h and those treated only for 24 h.

The increase in HVA concentrations after an oral dose of 1 mg kg^{-1} of haloperidol, taken over 24 h, did not seem to be as pronounced as after a subcutaneous dose of 0·2 mg kg^{-1} (Table 1, Kellogg & others, 1972). In the latter instance the animals were killed after 4 h, but we know from other studies that the increase in HVA concentrations after haloperidol lasts for at least 12–24 h (Andén & others, 1964). The oral administration route was used in the present study to avoid disturbing mothers and young.

The increase in HVA content after oral haloperidol was less pronounced in the infants' brains than in their mother's brain. This is unlikely to be due to a slow uptake of haloperidol into breast milk, because the same observation has previously been made after subcutaneous administration of haloperidol (Kellogg & others, 1972) and has been interpreted as due to the immaturity of the young animal's dopaminergic system. Also, there does not seem to be any accumulative effect of the drug since no difference was observed between the 72 and 24 h treatment.

In conclusion, administration of haloperidol to nursing rabbit mothers causes an increased HVA content in the brains of both the mothers and their nursing infants, indicating that significant amounts of the drug or an active metabolite can pass into the milk and reach the nursing infants.

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The fate of [^{14}C] lactose administered into the lungs of rats and monkeys

Disodium cromoglycate (cromolyn sodium) used in the treatment of asthma is administered as an aerosol powder into the respiratory tract. To improve the flow properties of the powder it is combined with 50% by weight of lactose (Intal).* Lactose administered orally is hydrolysed by intestinal β-D-galactosidase (Weser, Sleisenger & others, 1967) but the lung apparently lacks significant amounts of this enzyme (Cohen, Tsou & others, 1952). We have therefore investigated the fate of lactose administered intratracheally to rats (as a solution) and to monkeys (as a powder aerosol).

Two rats (CSE Ash, Spraque-Dawley derived, female, 225g) were anaesthetized with sodium pentobarbitone. Lactose, 2·5 mg (5 μCi) (D-glucose-[1-^{14}C] the Radiochemical Centre, Amersham, England) in 0·1 ml of water, was intubated into the trachea and as far into the bronchial tree as possible. The animals were allowed to recover in Metabowl† cages where they were kept for 24 h. Food and water were provided and the air flow was kept steady. Exhaled CO_2 was absorbed with ethanolamine in ethylene glycol monomethyl ether (1:2 v/v) contained in two Dreschel bottles in series. The $^{14}CO_2$ produced was determined by liquid scintillation counting and accounted for less than 1% of the dose.

Peak $^{14}CO_2$ exhalation occurred between 1 and 2 h after administration. Since absorption from the lung occurred rapidly it seems likely that the $^{14}CO_2$ was a product of general metabolism of lactose throughout the body rather than metabolism of lactose in the lung. Finely chopped fresh rat lung tissue (250 mg) was incubated at 37° in air with [^{14}C] lactose in Warburg flasks using Krebs-Ringer phosphate buffer at pH 7·4. The CO_2 produced was collected in alkali and the ^{14}C content determined. The $^{14}CO_2$ produced in 70 min was less than 0·5% of the radioactivity added indicating that little lactose metabolism occurred *in vitro*. Tissue viability was confirmed by normal oxygen uptake.

Tracheal and carotid arterial cannulae were inserted into four rats (male, 340–370 g) anaesthetized with sodium pentobarbitone. Each animal received heparin (5 mg) intra-arterially followed by 0·5 mg [^{14}C] lactose directly into the trachea as

* 'Intal' is the registered trademark of Fisons Ltd. It contains disodium cromoglycate and lactose (1:1 w/w).

† Jencons Ltd., Hemel Hempstead, U.K.