pituitaries containing a mean activity equivalent (± SD) to 67.73 ± 2.27 µg Tiapride/g fresh weight, the corresponding mean blood concentration (± SD) being 13.45 ± 0.74 µg/ml. Pituitary activities fell rapidly and were near blood levels (< 5 µg/ml) at 4 h after administration.

Assay of pituitary fragments (table) and autoradiography (figure 1) indicated an even distribution of Tiapride throughout the pituitary gland during the 1 h after administration. 1 h later, the activity in the neurohypophysis and adenohypophysis declined markedly, but there was some retention of label in the intermediate lobe (figure 2). The same distribution was observed until 6 h after drug administration, but with much diminished activity (autoradiograms required 3 months exposure) and at 24 h the localization was no longer detected. These studies also revealed the presence of ^{14}C in the parotid, submaxillary and sublingual salivary glands (figure 2) and the choroid plexus of the brain.

Pituitary and blood Tiapride levels based on ^{14}C-activity 30 min after an intramuscular injection of 50 mg/kg to female rats

Rat No.	µg Tiapride/g fresh tissue or ml of blood			
	Blood	Right lobe of adenohypophysis	Left lobe of adenohypophysis	Neurohypophysis / pars intermedia
1	15.10	57.57	55.56	64.51
2	12.10	52.46	49.98	56.48
3	10.49	48.55	47.15	51.92

Discussion. Several substituted benzamides including sulpiride have distinct effects on the mammary glands and genital tract of the rat[8], whilst sulpiride has no such effects in hypophysectomized male and female rats[9]. These observations suggest that these drugs have a direct effect upon the pituitary gland, and this is further supported by the finding that sulpiride and 2 other substituted benzamides, sultopride and metoclopramide, produce distinct histological changes in the adenohypophysis of the rat after prolonged treatment[8]. The present finding that Tiapride localizes in the pituitary gland is also consistent with the direct action of these drugs in this site.

The pars intermedia, which lies between the residual cleft and the neurohypophysis, is an endocrine gland, and much speculation has been reported concerning its function and significance in mammals[10]. It is believed to secrete a number of hormonal substances and to be associated with response to thirst[11], sodium depletion[12], and the experimental convulsion states produced by strychnine sulphate poisoning[13].

Thus the investigation of the action of Tiapride and possibly other substituted benzamides upon the above responses could throw some light upon the functions of pars intermedia.

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Methadone and brain development

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Summary. The effect of maternally administered methadone hydrochloride (5 mg/kg) on brain development of offspring treated during gestation and/or lactation was studied in 21-day-old rats. Animals treated during gestation or lactation were the most severely affected, with reductions in brain weights (12% and 30%, respectively), and DNA values (50% and 34%, respectively) observed.

Methadone is a synthetic narcotic analgesic that is commonly used in detoxification and maintenance programs for narcotic-addicted pregnant women[2]. Children delivered by methadone-exposed mothers often have retardation in body growth[3,4] and exhibit behavioral abnormalities[3]. Animal studies have shown that offspring maternally subjected to methadone may have congenital malformations of the central nervous system[5,6] and abnormal body growth[7–9]. The timing and duration of opiate treatment appear to be important factors in governing neurobiological response[9]. Rat pups maternally treated with methadone during gestation and/or lactation have altered patterns of brain development as determined by wet weight and macroscopic measurements[9]. At weaning (day 21), significant reductions in brain weights were only observed in those animals treated during either gestation or lactation. The present study was undertaken in order to ascertain if this impairment in brain growth is also accompanied by a reduction in neural cellularity.

Materials and methods. Female (180–200 g) Sprague-Dawley rats, housed under controlled conditions[8,9] with food and water ad libitum, were treated daily (8.00 h) with an i.p. injection of either 5 mg/kg dl-methadone hydrochloride (Dolophine, Eli Lilly Co., Indianapolis, Indiana) or an equivalent volume of physiologic saline. 5 days after the beginning of treatment, females were mated and sperm positivity indicated day 0 of gestation. Within 4 h after birth, litters of methadone-treated mothers were either transferred into cages with control mothers or placed with other methadone-injected mothers; these 2 groups of pups were considered to have been subjected to methadone during 'gestation alone' or given a combined 'gestation-lactation' treatment, respectively. A third group of pups delivered by control females were placed with methadone-injected mothers and were considered to be exposed to methadone during 'lactation alone'. Appropriate saline-injected 'controls' were included for each group. Litter size was maintained at 8 pups per mother, with an equal distribution of males and females.

All offspring were sacrificed by decapitation on day 21 and whole brains were removed and weighed. Brain tissues were homogenized in 1.4 M sucrose, and lipids extracted successively with chloroform-methanol (2:1,

v/v), 95% ethanol, and 5% trichloroacetic acid[10]. Homogenate samples were then hydrolyzed for 2 h with 0.6 N KOH and RNA was removed by precipitation with 1.2 N perchloric acid. DNA was determined by the diphenylamine reaction of Burton[11] and spectrophotometrically estimated as the difference in absorbance at 610 and 650 nm. Significant differences between control and experimental animals were assessed by the Student's t-test.

Results. Body weights (table) for all methadone-treated animals were significantly less than controls, with experimental animals weighing about 80% of saline-injected rats. Brain weight (table) were reduced in rats treated during gestation (12%) or lactation (30%), but were comparable to control values in animals exposed during gestation and lactation. Brain DNA-values were reduced in all methadone-treated animals (table). Drug exposure during gestation decreased DNA content by 50%, while a 34% reduction was noted in offspring treated only during lactation. Animals in the gestation-lactation group had reduced (but not significant) DNA-values.

Weights and DNA-composition of whole brains from 21-day-old rats subjected to different schedules of methadone

Methadone treatment	Body weight (g)	Brain weight (g)	DNA (mg/brain)
Control	51.25 ± 1.18	1.61 ± 0.56	2.22 ± 0.03
Gestation	37.00 ± 0.47*	1.41 ± 0.07*	1.10 ± 0.00*
Lactation	40.58 ± 0.97*	1.12 ± 0.03*	1.46 ± 0.00*
Gestation-lactation	40.11 ± 3.14*	1.56 ± 0.02	2.14 ± 0.05

Values for weights represent means ± SE for 10 animals per group. DNA-values represent means ± SE for quadruplicate samples from 4 assays per group. * Significantly different from controls at $p < 0.05$.

Discussion. Perinatal exposure to methadone produces decreases in the amount of DNA present in the brains of drug-exposed rat pups, with significant reductions observed in animals treated during gestation or lactation. Since estimations of the DNA content in brain tissues provide a useful measure of cell number[12], this retardation in brain growth in methadone-exposed animals appears to be accompanied by a reduction in neural cells. At this time it is difficult to determine which neural cells are involved in these cell losses, however neurogenesis is nearly completed in the rat brain by day 21[13], so that these decreases in cell number probably include neuronal deficits. Although it is not known whether perinatal exposure to methadone in humans has the same deleterious effects as in rats, it is interesting to note that infants delivered by methadone-treated mothers have a retardation in body growth[3,4], head circumference measurements below normal[4], and behavioral abnormalities during the first 2 years of life[3].

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Effects of palytoxin on the electrical activity of dog and rabbit heart[1]

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Summary. Reversible effects of palytoxin, extracted from colonies of the soft coral *Palythoa caribaeorum*, are described. There is a decrease of both membrane resting potential and overshoot during activity. Rise time of the action potential is prolonged, while repolarization is shortened. The electrical events resemble those seen with metabolic poisons.

Palythoa caribaeorum, a soft coral (coelenterate) found in shallow waters on the shores of the Caribbean Islands, contains a highly toxic substance which has been extracted, purified, and partially characterized[3,4]. These carnivorous animals hold their prey by protruding cell organelles (nematocysts) and by releasing their powerful toxin to paralyze their prey. Toxicity of various fractions of the crude extract is usually measured by noting the survival time of mammals[5,6] or small fishes[7]. Thus, the i. v. LD_{50} of a highly purified toxin is 0.025 µg/kg for rabbit[6]. The partially purified material available to us killed a dog when injected i. v. at a dose of 5 µg/kg[8]. My own interest in palytoxin started when it had become evident that ventricular trabeculae from poisoned dog hearts could be used for in vitro experiments of a different kind. The apparent phenomenon of reversibility of palytoxin effects prompted me to look for possible modes of action.

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