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PHYSIOLOGIC DISPOSITION OF [^{3}H]EPINEPHRINE IN THE RABBIT FETUS

EFFECT OF PROMETHAZINE*

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Abstract—[^{3}H]epinephrine was injected into fetal rabbits through the uterine wall on day 26 of gestation in order to study placental transfer, and the uptake, retention and metabolism of the hormone in fetal tissues. Less than 0.1 per cent of the administered [^{3}H] was found in maternal blood or within uninjected littermates. Accumulation of [^{3}H]/g of tissue was greatest in the fetal kidney, liver and intestine, and less in the heart and lung. Levels of [^{3}H] in the fetal serum, heart, lung and placenta were comparable in value at 5 and 30 min, but all fell by 60 min. In contrast, the fetal kidney and intestine show a 2- to 4-fold accumulation of [^{3}H] in 30 min as compared to 5 min, while the fetal liver exhibits a 10-fold accumulation over 30 and 60 min. [^{3}H] metabolites present in fetal serum at 30 min, expressed as a per cent of the total radioactivity, are 45 per cent for metanephrine and 27 per cent for *O*-methylated deaminated products, while 25 per cent is present as unmetabolized [^{3}H]epinephrine. *O*-methylated metabolites are predominant in the liver, where 85 per cent of the radioactivity comprises metanephrine in conjugated and unconjugated forms. Administration of promethazine to the doe prior to injection of [^{3}H]epinephrine into rabbit fetuses resulted in a 40–64 per cent decrease in accumulation of [^{3}H] in the fetal brain, liver, lung, kidney, intestine and heart. The pattern of metabolites in the serum of promethazine-treated fetuses shows an increase in the per cent of [^{3}H] in the *O*-methylated, deaminated fraction from 27 to 37 per cent. While the total per cent of *O*-methylated metabolite is not altered in the liver of treated fetuses, metanephrine is predominantly present in the conjugated form. The liver of the rabbit fetus is an important site for accumulation of catecholamine metabolites and is pharmacologically sensitive to promethazine administered to the mother.

The physiological disposition of catecholamines is a function of uptake, storage and metabolic processes either within adrenergic neurons or at extraneuronal sites [1]. Inactivation of catecholamines by tissues of the newborn rat differs significantly from the adult in that the retention of norepinephrine in most, but not all, newborn tissues is deficient [2]. Histochemical studies indicate that these differences reflect the considerable variation found in the rate of development of sympathetic innervation to various tissues [3, 4]. Current knowledge of the functioning of the adrenergic nervous system in the fetus is based mainly on histochemical studies and measurement *in vitro* of endogenous catecholamine stores and enzyme activities. Thus, nerve plexa of the heart of the neonatal rat and rabbit exhibit poor fluorescence and histochemical morphology, while those of the intestine show an adult pattern [3, 4]. The norepinephrine content in most tissues with sympathetic innervation is low during fetal life and reaches adult levels postnatally [2, 5]. Several phylogenetic studies indicate that a progressive increase in catecholamine content of the developing heart occurs in many species throughout gestation and neonatal life [2, 6, 7]. The mechanisms for uptake and storage of catecholamines are poorly developed in the heart [5] and brain [8] of fetal rats. Finally, the metabolic inactivation of catecholamines through monoamine oxidase (EC 1.4.3.4, MAO) and catechol-*O*-methyl transferase (EC 2.1.1.7, COMT) appears to develop with advancing age [9]. Because adrenergic receptors are reported to be functional at an early age in the fetus [10, 11] and because the titers of epinephrine and norepinephrine in the fetal circulation of the rabbit are comparable to the maternal blood concentration [12], it is essential to understand the mechanisms for inactivation *in vivo* of circulating catecholamines in the fetus. Such knowledge is necessary to elucidate the fetal response to stress and the potential interaction of pharmacologic agents with these mechanisms.

Our present studies involve the injection of [^{3}H]epinephrine directly into the fetal rabbit in order to study placental transfer and the uptake, retention and metabolism of the hormone in fetal tissues. In view of the anesthetic and therapeutic use of promethazine [1,(2-deimethyaminopropyl) phenothiazine] during pregnancy [13, 14], the effect of administration to the mother of this phenothiazine on the disposition of fetal catecholamines was investigated.

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MATERIALS

Cellulose MN 300 and thin-layer chromatography (t.l.c.) supports were purchased from Brinkman Instruments (Canada). Alumina (Woelm) neutral activity, grade I, was acid washed and heated according to the method of Crout [15]. Cation exchange resin AG50W-X8 (200–400 mesh) was obtained from BioRad Laboratories. Organic solvents were obtained from A & C Chemical Co. (Montreal) and redistilled. Scintiverse was purchased from Fisher Scientific Co., catecholamine standards from Sigma Chemical Corp., Glusulase from Endo Laboratories and NCS tissue solubilizer from Amersham Searle. Promethazine–HCl (Phenergan) was purchased from Pouleric (Montreal). All other chemicals were analytical reagent grade and used as purchased.

METHODS

Radioactive compounds. *dl*-Epinephrine[7-^{3}H]bitartrate (10 Ci/m-mole) and *dl*-epinephrine[7-^{14}C]bitartrate (48 mCi/m-mole) were obtained from New England Nuclear Corp. (Canada), Montreal, Quebec. The purity of both radioisotopes was ascertained by chromatography on t.l.c. on cellulose MN 300 plates using the solvent systems of *n*-butanol–glacial acetic acid–water (4:1:1 v/v) and isopropanol saturated with 1 N HCl. In both systems the labeled epinephrine migrated as a single radioactive peak with no other labeled impurities. [^{3}H]epinephrine was always used within 1 month of receipt. Non-labeled standards were visualized on t.l.c. plates with the diazotized *p*-nitroaniline spray.

Animals. New Zealand white rabbits, on day 26 of gestation, were laparotomized under local anesthesia using 1% lidocaine HCl. The animals were manually restrained and the lidocaine was injected i.m. prior to laparotomy. The animals were relaxed and not hyperventilating during the 30 min of this procedure. One uterine horn was exteriorized, and [^{3}H]epinephrine, 5 μCi (100 ng) in 0.1 ml was injected through the uterine wall into the flank of each of five to six fetuses. The administered dose of epinephrine was close to physiological based on the data of Dawes *et al.* [16]. The hindquarters of the fetus were easily visualized through the uterine wall so that the injection site was readily identified. The uterine horn was carefully replaced within the abdomen and the incision closed with hemostats. After time intervals of 5, 30 and 60 min, the fetuses were removed and decapitated. Fetal blood was immediately collected in chilled tubes and fetal tissues were excised and frozen rapidly in acetone–dry ice until further analysis. Promethazine, 12.5 mg/kg, was given i.v. to the doe 20 min prior to laparotomy.

Determination of radioactivity. Tissues were trimmed and weighed. The placenta was separated into maternal and fetal portions and lumenal contents were removed from the intestine. Aliquots of 100–200 mg were solubilized overnight in 2 ml of NCS solubilizer and radioactivity was determined using a Packard Tricarb spectrometer (model 3003) after addition of 15 ml Omnifluor (New England Nuclear Corp.) solution (8 g/liter). The quenching and counting efficiency were determined by the use of automatic external standardization (a.e.s.). Quench correction curves (a.e.s. vs per cent efficiency) were obtained from each tissue using at least six tissue samples ranging from 25 to 200 mg. A sufficient number of counts were accumulated to give standard errors of counting of less than 1 per cent.

All aqueous samples (0.2 to 0.5 ml) were counted using 15 ml Scintiverse. Labeled catecholamines run on t.l.c. plates were visualized by scanning with a Packard model 7200 Radiochromatogram scanner. The method of Okita *et al.* [17] was used to calculate [^{3}H] and [^{14}C] in samples containing both labels. Internal standards of [^{3}H] and [^{14}C] were used to determine the efficiency of counting under these conditions.

Metabolites. The frozen tissues were partially thawed, weighed and homogenized in 5 vol. of ice-cold 0.4 M perchloric acid (PCA) containing 1% EDTA. After centrifugation for 20 min at 10,000 *g*, the supernatant was set aside and the pellet was re-homogenized in 3 vol. PCA–1% EDTA. To the combined supernatant fraction was added 10 mg sodium metabisulfite along with the following non-labeled metabolites: epinephrine, metanephrine (MN), 3,4-dihydroxymandelic acid, 3-methoxy-4-hydroxy-mandelic acid and 3-methoxy-4-hydroxyphenylglycol (MHPG), all in the concentration of 100 μg/g wet weight tissue. The pH of this solution was adjusted to 4.5 with potassium hydroxide (5 and 0.5 N), chilled for 1 hr and the resulting potassium perchlorate precipitate was removed by centrifugation. This tissue extract was used for the quantitation of epinephrine and metanephrine. At this stage, recovery of total tissue radioactivity was 55–65 per cent. The conjugated metabolites of epinephrine were hydrolyzed with a mixture of β-glucuronidase and sulfatase (Glusulase). An aliquot of the above tissue extract was buffered with an equal volume of 0.5 M sodium acetate (pH 6.0), and 0.02 vol. Glusulase was added. The mixture was incubated at 37° for 24 hr. Then 0.2 ml of 2% ascorbic acid was added and the solution applied directly to an alumina column as described below for tissue extracts.

Epinephrine was separated from its metabolites by adsorption on alumina using the method of Crout [15]. To the tissue extract were added 10 ml of 0.2 M sodium acetate, 0.2 ml of 2% ascorbic acid and 0.5 g alumina. When serum was analyzed, 0.5 ml of 0.2 M EDTA was also added. The pH was adjusted to 8.4 to 8.5 with sodium hydroxide (5 and 0.5 N) using constant stirring for 3–4 min. The mixture was then quantitatively transferred to a glass column (0.9 × 16 cm) and the alumina washed with 10 ml water. The initial effluent and the water wash were combined and used for the determination of MN. Then 20 ml of 0.2 N acetic acid (HAc), followed by 20 ml of 1 N HAc, was percolated through the column in order to elute the labeled epinephrine. [^{14}C]epinephrine was added as an internal recovery marker when serum was analyzed. Recovery of [^{14}C]epinephrine in the 0.2 N HAc fraction varied between 76 and 90 per cent with less than 10 per cent of labeled material appearing in the initial effluent. When the 0.2 N HAc fractions of serum were pooled and chromatographed on t.l.c. using the solvent system *n*-butanol saturated with 1 N HCl, a single radioactive peak was observed which

Table 1. Distribution of radioactivity after injection of [^{3}H]epinephrine into fetal rabbits*

Time (min)	Injected fetus serum (dis./min/ml)	Uninjected fetus serum (dis./min/ml)	Uninjected placenta (dis./min/g)	Maternal serum (dis./min/ml)
5	292,390 ± 23,800 (10)	0 (5)	550 ± 200 (10)	0 (2)
30	266,290 ± 18,200 (15)	600 ± 100 (8)	150 ± 50 (8)	2,400 ± 400 (4)
60	149,220 ± 7,500 (5)	900 ± 100 (4)	950 ± 300 (8)	3,560 (1)

* [^{3}H]epinephrine [5 μCi (100 ng)/fetus] was injected through the uterine wall into the flank of five fetal rabbits/litter. Each value represents the mean ± S.E.M. of the number of fetuses shown in parentheses and includes injected and uninjected littermates which were determined from a total of seven litters.

migrated with the mobility of the epinephrine standard.

Unconjugated metanephrine was isolated from the effluent of the alumina column using a cation exchange resin according to a modification of the method of Kopin *et al.* [18]. BioRad AG50W-X8 (200-400 mesh) was converted to the sodium form and stored in 0.1 M sodium potassium phosphate (pH 6.0). A 1-cm resin bed was poured into a 0.9 × 16 cm glass column and was washed with 20 ml water. The initial effluent of the tissue extract applied to the alumina column was passed through the resin and this was followed by a 20-ml water wash. Unconjugated metanephrine was then eluted with 25 ml of 3 N ammonium hydroxide. The recovery of ^{3}H-labeled material applied to the column was 95–99 per cent. When the sample was hydrolyzed with Glusulase, the effluent and wash from the cation exchange resin were designated as the *O*-methylated, deaminated metabolite fraction. This fraction contained only vanylmandelic acid (VMA) and MHPG when non-labeled standards chromatographed on the column were run on t.l.c.

RESULTS

Placental transfer of [^{3}H]*epinephrine.* In our initial experiments we wished to determine the extent to which [^{3}H]epinephrine injected into the fetus would pass to uninjected littermates and to the maternal circulation. To accomplish this, 5 μCi [^{3}H]epinephrine was injected into the fetal rabbits and blood was collected from the mother by heart puncture and from uninjected littermates in both uterine horns. The results obtained are shown in Table 1. From these data it is evident that less than 0.1 per cent of the administered radioactivity was found in sites other than the injected fetuses. The accumulation of radioactive material in the serum of the uninjected littermates, placenta and in the maternal serum seems to be time dependent in the 60 min studied. Because no appreciable radioactivity crossed the rabbit placenta, we considered that each injected fetus could be used as a separate entity for uptake and metabolism studies.

Tissue distribution of radioactivity. The relative concentration of radioactivity in various organs of the fetal rabbit was measured 30 min after the injection of [^{3}H]epinephrine into the fetus. In Fig. 1 are shown both the concentration of radioactivity and the percentage of the administered dose found in each organ. It is apparent that the data expressed in this way are not well correlated, in that the portion of [^{3}H] found in an organ is a function of organ size as well as its ability to concentrate radioactivity. Because of the large number of observations made which allow statistical analysis, it is possible to compare the relative net tissue uptake of injected [^{3}H]epinephrine. Tissues showing the greatest ability to accumulate [^{3}H]/g are kidney, liver and intestine, while the heart

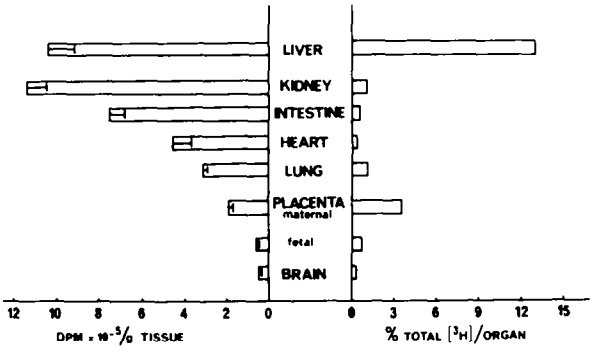

Fig. 1. Tissue distribution of [^{3}H] 30 min after injection of [^{3}H]epinephrine into fetal rabbits. Radioactivity per g of tissue is expressed as the mean ± S.E.M. of organs from fifteen fetuses. Total [^{3}H]/organ is expressed as the per cent of [^{3}H] injected into each rabbit fetus.

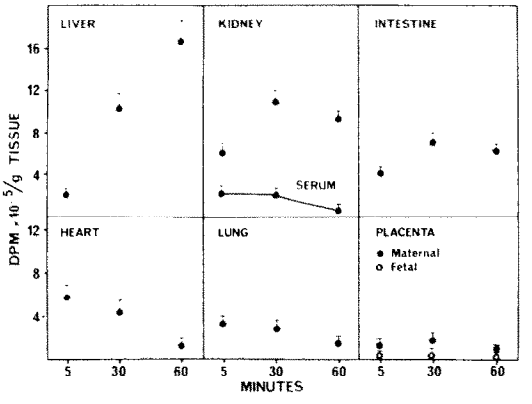

Fig. 2. Time course of [^{3}H] accumulation in various fetal tissues after injection of [^{3}H]epinephrine into fetal rabbits. Values are expressed as the mean ± S.E.M. of [^{3}H] in tissues from ten fetuses at 5-min, fifteen fetuses at 30-min, and five fetuses at 60-min intervals.

and lung are less efficient. It is noteworthy that the maternal placenta, the highly vascular portion of this organ, has a much greater accumulation than the spongy, white fetal placenta. Although some radioactivity is found in the brain, pointing to the passage of [^{3}H]epinephrine across the blood–brain barrier, the concentration in the whole brain is relatively small. When the per cent of injected dose is examined, the most prominent organ with the ability to accumulate circulating catecholamine is the liver (13 per cent), with the maternal placenta (3.5 per cent) also playing an important role.

Time course of [^{3}H]*accumulation.* The accumulation of radioactivity during 60 min after the injection of [^{3}H]epinephrine into the fetus is shown in Fig. 2. It is possible that an initial high level of radioactivity observed at 5 min may more accurately reflect the proportion of cardiac output delivered to the fetal organ than the ability of that tissue to concentrate catecholamine. Conversely, accumulation over a 30- and 60-min period better reflects the capacity of a tissue to retain radioactive material. Serum levels of [^{3}H] were comparable at 5 and 30 min and declined somewhat at 60 min, a time course comparable to accumulation in the lung and placenta. The heart showed a progressive decline in ability to retain radioactivity between 5 and 60 min. The kidney and intestine exhibit a different pattern in that a 2- to 4-fold accumulation of [^{3}H] was observed between 5 and 30 min, followed by a slight decline at 60 min. By contrast the liver has a highly significant 10-fold accumulation of radioactivity over a period of 30 and 60 min, suggestive of an active sequestration process in the face of unchanged or declining levels of [^{3}H] in other fetal tissues.

Effect of promethazine. Promethazine is an antihistaminic phenothiazine widely used as preoperative medication in obstetrical anesthesia. In our initial studies promethazine was given to the doe as a sedative prior to laparotomy. When laparotomy was performed without promethazine, we found that the drug affected the accumulation of [^{3}H]epinephrine by fetal tissues. The results obtained from these studies, 30 min after injection of labeled hormone, are shown in Fig. 3. Concentrations of radioactivity in the serum, heart and placenta from treated animals were not significantly different from controls. By contrast, a highly significant decrease in the accumulation of [^{3}H] was found in the brain, lung, liver, kidney and intestine of treated fetuses. The depression in levels of radioactivity compared to control values ranged from 65 per cent for the intestine to 40 per cent for the lung.

If tissue levels of [^{3}H] are viewed as an integral of uptake, storage and/or metabolism, and efflux of the hormone and metabolites, it was then necessary to determine if catecholamine metabolism was altered by administration of promethazine. The results from such studies are shown in Table 2. In control animals, unmetabolized epinephrine comprises 25 per cent of the radioactivity in the serum but less than 1 per cent in the fetal liver. MN comprises 45 per cent of the label in the serum, which suggests that *O*-methylation is the predominant metabolic route for [^{3}H]epinephrine metabolism. This is confirmed in the fetal liver of untreated animals where [^{3}H]epinephrine is completely metabolized with 83 per cent of the radioactivity comprising *O*-methylated products in the conjugated and unconjugated forms. The MN conjugate is not found in the serum fraction. The *O*-methylated deaminated metabolites of epinephrine in the serum and liver of control animals are 27 and 16 per cent of the total radioactivity respectively. These data suggest that the fetal liver may play an important role in the inactivation of circulating catecholamines.

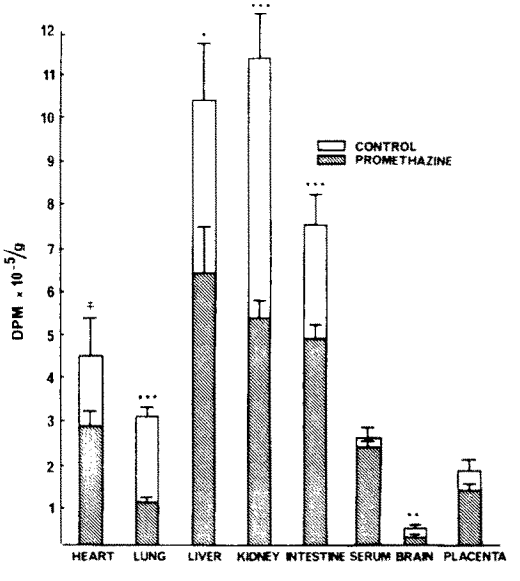

Fig. 3. Effect of promethazine on [^{3}H] accumulation in fetal rabbit tissues 30 min after injection of [^{3}H]epinephrine. Promethazine (12.5 mg/kg) was given i.v. to the doe 20 min prior to laparotomy. Values are expressed as the mean ± S. E. M. of tissue from fifteen control and eleven promethazine-treated fetuses. Statistical comparisons were calculated using the Student's '*t*' test on unpaired determinations. Key: ‡, $P < 0.1$; *, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$.

Table 2. Effect of promethazine on metabolism of [^{3}H]epinephrine in the rabbit fetus*

	Total [^{3}H] (dis./min)	Total [^{3}H] (%)			
			Metanephrine		
		Epinephrine	Unconjugated	Conjugated	*O*-methylated deaminated
Serum					
Control (6)	171,150 ± 18,800	25 ± 2	45 ± 2	0	27 ± 2
Promethazine (12)	130,600 ± 6,900	19 ± 1†	42 ± 3	0	37 ± 3‡
Liver					
Control (5)	418,380 ± 121,390	1	47 ± 2	36 ± 2	16 ± 1
Promethazine (6)	516,590 ± 101,250	1	18 ± 2§	57 ± 6§	25 ± 6

* Each value represents the mean ± S.E.M. of the number of determinations shown in parentheses, each sample comprised of tissue pooled from one to three fetuses to obtain adequate dis./min for metabolite separation. Conjugated MN was determined by the difference between MN fractions before and after hydrolysis with Glusulase. Statistical comparisons were by Student's '*t*' test using unpaired determinations.

† $P < 0.1$.

‡ $P < 0.01$.

§ $P < 0.001$.

In the serum of promethazine-treated animals, there is a 5 per cent decrease in the per cent of [^{3}H]epinephrine, while the proportion of MN remains unchanged. By contrast the per cent [^{3}H] in the *O*-methylated, deaminated fraction is significantly increased from 27 per cent in controls to 37 per cent in treated fetuses ($P < 0.01$). The pattern of metabolites in the liver of treated animals is similar to controls in that [^{3}H]epinephrine is completely metabolized, predominantly by *O*-methylation to MN. In contrast, a far greater proportion of MN is in the conjugated form in the liver of treated animals and appears to be retained in this organ because none is present in the serum.

DISCUSSION

The placental transfer of catecholamines has been a subject of much controversy in recent years. A limited transfer of radioactive norepinephrine from the maternal to the fetal circulation has been reported by some investigators in the human and guinea pig [19], while other workers report no such passage in the human [20] and the rat [5]. Such studies are complicated by the possibility that administration of catecholamines to the mother during pregnancy may cause vasoconstriction of the utero-placental circulation, thereby altering placental perfusion [21]. Cession [22] observed that a pharmacologic dose of [^{3}H]epinephrine given to the pregnant rabbit fails to cross to the fetal circulation primarily because of extensive metabolism in maternal tissues and the placenta. Saarikoski [20] tried to minimize these complications by injecting labeled norepinephrine into the umbilical vein of the pre-viable human fetus while the fetoplacental circulation remained intact. Unfortunately these studies were performed under general anesthesia with drugs known to cross the placenta [23]. Our experiments were designed to minimize these problems insofar as only a local anesthetic was used and the fetuses were injected through the uterine wall. Our data indicate that an insignificant amount of [^{3}H]epinephrine injected into the rabbit fetus reaches the maternal circulation.

The data presented here on the distribution of injected [^{3}H]epinephrine in fetal rabbit tissues indicate that the liver is the primary site of uptake of radioactivity (see Fig. 1), followed by the placenta and, to a lesser extent, the lung and kidney. Saarikoski [20] reported a similar tissue distribution in the pre-viable human fetus after injection of [^{3}H]norepinephrine into the umbilical vein. The distribution of [^{3}H] in fetal rabbit tissues is markedly different from that found in the adult cat [24] and rat [25]. In these species, the heart accumulates far more radioactivity than the liver, despite the vast difference in organ size. The pattern of catecholamine accumulation in the rabbit fetal tissues is strikingly similar to that found in immunosympathectomized rats in whom the administration of nerve growth factor antiserum at birth produced an almost complete inhibition of normal sympathetic innervation to the heart [25]. The presence of measurable quantities of [^{3}H] in fetal rabbit brain is consistent with the relative permeability of the blood–brain barrier toward circulating catecholamines which has been demonstrated in newborn rats [26].

Although blood levels of radioactivity are not different at 5 and 30 min, the fetal rabbit liver, kidney and intestine show a significant accumulation of label over a 30-min interval. Gershon and Thompson [4] recently studied the ontogeny of norepinephrine uptake in the fetal rabbit intestine and found the onset of specific uptake occurred after day 21 of gestation. In this study, we found the injected [^{3}H]epinephrine was completely metabolized, and in the fetal rabbit liver the major metabolite found was metanephrine (see Table 2). These findings are consistent with values reported for COMT and MAO activity in fetal rabbit tissues [27]. Furthermore, the extent of catecholamine uptake and metabolism is comparable to that found in the perfused liver of the adult rat [28]. The substantial conjugation of metanephrine found in the fetal rabbit liver was unexpected because conjugation of a variety of substrates in the liver of newborn rabbits has been reported to be 15–25 per cent of that found for adult tissues [29]. In view of the absence of conjugated metanephrine in fetal serum and the continued accumulation of [^{3}H] in the liver for 60 min, it appears that the fetal

rabbit liver is not releasing conjugated metabolites into the circulation.

The heart of the fetal rabbit exhibits a progressive decline in radioactivity from 5-min levels, indicating the mechanisms of catecholamine accumulation in this organ appear to be very poorly developed during late gestation. Deficiencies in both uptake and retention of catecholamines have been described in the neonatal rat heart [2, 26]. Atwood and Kirshner [30] conclude that the increasing ability of developing rat heart to accumulate norepinephrine is due to an increasing number or storage capacity of synaptic vesicles. Mirkin [5] suggests that the onset of binding capacity is correlated with the appearance of a discrete soluble protein within the adrenergic neuron shortly after birth.

Promethazine is an antihistaminic phenothiazine used during pregnancy for its antiemetic, sedative and narcotic potentiating effects [13, 14]. Transplacental passage of promethazine has been demonstrated in mice [31] and is thought to occur in humans where terapeutic administration of the drug is associated with congenital malformation and immunosuppressive effects in newborn infants [13, 14]. Our data indicate that the administration of promethazine to the pregnant rabbit is associated with a striking decrease in distribution of [^{3}H] in fetal tissues after injection of [^{3}H]epinephrine into the fetus (see Fig. 3). If promethazine acts by interfering directly with the disposition of fetal catecholamines, the observed changes in [^{3}H] accumulation may reflect alterations in hormone uptake, metabolism and efflux from tissues. The data presented here do not allow us to discriminate among these various possibilities. The amount of total radioactivity as well as the per cent of [^{3}H]epinephrine in serum was not significantly different between treated and control animals. It is noteworthy that while [^{3}H] accumulation in the livers of treated animals is 61 per cent of control values, the effect of promethazine on the hepatic metabolites of [^{3}H]epinephrine was primarily to shift metanephrine from the unconjugated to the conjugated form.

The data presented here are in accord with the ontogenetic development of catecholamine uptake and retention processes which have been previously associated with development of the sympathetic nervous system in the rat [2, 5]. Thus, the heart of the rabbit fetus lacks the ability to accumulate epinephrine during late gestation when adrenergic innervation to this organ is poorly developed [7]. Because hepatic metabolism appears to be the most important route for inactivation of [^{3}H]epinephrine, the fetal rabbit seems to be primarily dependent on extraneuronal mechanisms for disposition of circulating catecholamines. Our observation that significant amounts of radioactivity are accumulated in fetal intestine, kidney and lung warrants further study to determine if the [^{3}H] is present as metabolites or stored as unchanged epinephrine.

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