Contribution of lungs to desipramine-induced changes in whole body catecholamine kinetics in newborn lambs

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Smolich, Joseph J., Helen S. Cox, and Murray D. Esler. Contribution of lungs to desipramine-induced changes in whole body catecholamine kinetics in newborn lambs. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R243–R250, 1999.—To characterize pulmonary and total body norepinephrine and epinephrine kinetics in the immediate newborn period, the effects of desipramine were studied in six fetal lambs chronically instrumented at 133–134 days gestation (term 147 days) and delivered 1 wk later by cesarean section under spinal anesthesia. Norepinephrine and epinephrine kinetics were determined with isotope dilution methodology 4 h after birth and repeated 30 min after desipramine (2 mg/kg iv). At baseline, the lungs accounted for 35 ± 10 and 47 ± 13% of whole body norepinephrine clearance (93 ± 8 ml·min−1·kg−1) and spillover (188 ± 29 ng·min−1·kg−1) and 15 ± 2 and 19 ± 7% of whole body epinephrine clearance (82 ± 4 ml·min−1·kg−1) and release (22.7 ± 2.7 ng·min−1·kg−1), respectively. Desipramine decreased pulmonary norepinephrine and epinephrine clearance and spillover to near-zero levels, whereas whole body norepinephrine clearance fell by 51 ± 3% (P < 0.001), norepinephrine spillover by 54 ± 6% (P < 0.005), epinephrine clearance by 30 ± 6% (P < 0.01), and epinephrine spillover by 34 ± 11% (P < 0.05). These results indicate that, in the immediate newborn period, pulmonary removal and release of norepinephrine and epinephrine is mediated by a desipramine-sensitive process that accounts for a major portion of associated reductions in whole body norepinephrine and epinephrine clearance and release.

Recent findings from studies done in this laboratory employing isotope dilution methodology in chronically instrumented fetal lambs before and after delivery have provided new insights into the kinetics of the catecholamines norepinephrine and epinephrine in the immediate newborn period. Thus whole body studies indicated that about one-half of the birth-related surge in circulating catecholamines is related to increased norepinephrine and epinephrine release into the circulation associated with enhanced sympathoadrenal activity and the remainder to reduced catecholamine clearance from the circulation accompanying loss of the placenta (36). Subsequent pulmonary studies suggested that the lungs make a substantial contribution to whole body catecholamine kinetics after birth, accounting for approximately one-third of total body norepinephrine and one-tenth of total body epinephrine clearance from the circulation, as well as up to two-fifths of total body norepinephrine and up to one-fifth of total body epinephrine release into the circulation (37).

In the adult, considerable information is available about factors that modulate norepinephrine and epinephrine clearance and release (10, 12–21, 28, 29, 40, 41) and this has facilitated increased understanding of disturbances in sympathoadrenal function accompanying disease processes (17). By contrast, relatively little is known about these factors in the setting of the incompletely developed sympathetic innervation characteristic of the immediate newborn period (27). In particular, it is unknown to what extent pulmonary and total body norepinephrine and epinephrine removal after birth is affected by the tricyclic antidepressant desipramine, which is a potent inhibitor of catecholamine uptake into sympathetic neurons (10, 15, 24) as well as the neuronal-like catecholamine uptake process located within the microvasculature of the lungs (4, 14). In addition, it is unknown if desipramine affects pulmonary or total body norepinephrine and epinephrine release into the circulation after birth, a question that is of particular relevance not only because desipramine has central sympathoinhibitory effects (15, 41) but also because birth is accompanied by increased central sympathoadrenal outflow (33). Furthermore, it is unclear to what extent pulmonary changes contribute to the whole body effects of desipramine on norepinephrine and epinephrine kinetics in the newborn.

Accordingly, the aim of this study was to examine the actions of desipramine on pulmonary and total body norepinephrine and epinephrine kinetics in the immediate newborn period. Experiments were performed in conscious, chronically instrumented near-term lambs 4 h after cesarean section delivery, a time point characterized by the presence of substantial pulmonary uptake and release of both norepinephrine and epinephrine (37). Pulmonary and total body norepinephrine and epinephrine kinetics were determined using a combined tracer infusion of 3H-labeled norepinephrine and epinephrine, while blood flows were measured with radioactive microspheres.

Materials and Methods

All experiments were approved by the Monash University Animal Experimentation Committee and were in accord with guidelines established by the National Health and Medical Research Council of Australia.

Animal preparation. Six fetal lambs with known breeding dates were chronically instrumented under aseptic conditions at 133–134 days gestation (term 147 days) as previously described (35–37). Briefly, fasted Border-Lleicester cross ewes were anesthetized with propofol (5 mg/kg iv), intubated, and then mechanically ventilated with 1–3% halothane and a 2:1 mixture of nitrous oxide and oxygen. The uterus was exposed through a midline laparotomy and incised over the fetal hindlimbs. Polyvinyl catheters (ID 1 mm, OD 1.5 mm) were inserted into a posterior tibial artery and lateral saphenous vein and advanced into the abdominal aorta and inferior vena cava.
cava, respectively. After delivery of the fetal head, left forelimb, and upper thorax through a second hysterotomy, a thoracotomy was performed in the third left interspace and the pericardium was opened over the pulmonary trunk and left atrium. A Teflon cannula connected to a polyvinyl catheter was inserted into the distal part of the pulmonary trunk, and a polyvinyl catheter was introduced into the left atrial cavity through a purse-string suture. The pericardium was then loosely closed, the ribs reapprised, and overlying muscle layers repaired. After ventral incision of the neck in the midline, a Teflon cannula attached to a polyvinyl catheter was inserted nonocclusively into the left carotid artery and a polyvinyl catheter was passed into the superior vena cava via the left external jugular vein. Both catheters were tunneled subcutaneously to the chest incision. A Silastic catheter (ID 0.8 mm, OD 1.7 mm) was inserted into the trachea and exteriorized through the cephalic end of the neck incision in all fetuses for later withdrawal of lung liquid. Finally, a wide-bore catheter was sutured to the anterior chest wall for measurement of amniotic fluid pressure. The fetus was then returned to the uterus, and all incisions were closed. The vascular catheters were filled with sodium heparin solution (1,000 IU/ml) and exteriorized on the right flank of the ewe. After surgery, vascular catheters were flushed every second day and refilled with sodium heparin. Antibiotics (500 mg streptomycin and 5 $\times$ 10$^6$ units penicillin) were instilled into the amniotic cavity perioperatively and then administered daily, either as an intramuscular injection to the ewe or directly into the amniotic cavity when catheters were flushed.

Experimental protocol. Seven days after surgery (i.e., at a gestation of 140–141 days), low spinal anesthesia was induced in the ewe with an intrathecal injection of 3–5 ml of 0.5% bupivacaine. After withdrawal of approximately 40 ml of lung liquid via the tracheal catheter to facilitate the rapid establishment of pulmonary gas exchange after birth (3), the fetus was quickly delivered by cesarean section delivery with an intravenous overdose of pentobarbitone sodium. All lambs breathed spontaneously and rapidly established a rhythmic breathing pattern.

The baseline catecholamine kinetics study was performed in newborn lambs 4 h after cord clamping, after the commencement of a continuous and constant-rate infusion of $^{3}$Hnorepinephrine and $^{3}$Hepinephrine via the hindlimb catheter 30 min beforehand. At baseline, hemodynamics were recorded; blood samples were taken for hematocrit, blood gas, and catecholamine analysis; and left ventricular (LV) output was measured with radioactive microspheres (22). Blood withdrawn during blood sampling and injection of radioactive microspheres was replaced with newborn lamb blood mixed 1:1 with a plasma substitute (Haemaccel, Behring, Marburg, Germany). Catecholamine neuronal uptake was then blocked in 0.8% for epinephrine. A representative chromatogram is shown in Fig. 1. Endogenous levels of norepinephrine and epinephrine were not corrected for the contribution of exogenous $^{3}$H-labeled catecholamines, because the latter comprised <1% of circulating norepinephrine and epinephrine levels both before and after desipramine.

Radioactive microsphere technique. Radioactive microspheres, 15 μm in diameter and labeled with one of five gamma-emitting isotopes ($^{113}$Sn, $^{89}$Sr, $^{99}$Nb, or $^{46}$Sc, New England Nuclear) were ultrasonicated for 10–15 min before injection and then injected over 30–45 s with 10 ml isotonic saline. About 0.5 × 10$^6$ microspheres were injected into the left atrium while reference samples were obtained from the carotid artery and the abdominal aorta. All reference samples were drawn at a rate of 4.1 ml/min with a mechanical pump (model 901A, Harvard Apparatus). Reference sample collection was commenced 5–10 s before injection and continued for an additional 75 s after the completion of the injection.

At the end of the experiment, lambs were killed on an intravenous overdose of pentobarbitone sodium and, at postmortem examination, the position of all catheters was carefully checked and the ductus arteriosus was confirmed to be markedly constricted. The lungs were placed in Formalin fixative for 7–10 days and then carbonized at a temperature of 280°C in a vented box furnace. The carbonized tissue was ground into a coarse powder and packed into plastic counting vials to a height of ≤2 cm. The radioactivity of the blood reference samples and the tissue vials was counted in a gamma counter (model 1282 CompuGamma, LKB-Wallac,
Calculation of catecholamine clearance and spillover. Total body plasma catecholamine clearance and spillover rates were obtained with previously described formulas (10–18). Thus total body plasma clearance of catecholamines (TBCl) was calculated as \( \frac{\text{IR}}{[\text{3H}\text{CatA}} \cdot \text{body wt.} \), where IR is the infusion rate of \([\text{3H}\text{CatA}}\) (dpm/min), \([\text{H}\text{CatA}}\) is the steady-state mean systemic arterial plasma concentration of \([\text{3H}\text{CatA}}\) (dpm/ml), and body weight is in kilograms. To obtain an accurate estimate of total body clearance, the infusion rate of \([\text{3H}\text{CatA}}\) was corrected for pulmonary catecholamine extraction (19, 21). The total body fractional extraction (TBFx) of either catecholamine, i.e., the proportion extracted on first passage through the circulation, was computed as \( \frac{\text{TBCl}}{[\text{3H}\text{CatA}}\cdot(1 - \text{Hct})\) where Hct is the hematocrit. The total body spillover rate of catecholamines into plasma was equivalent to \( \text{TBCl} \cdot \text{CatA}}\), where \([\text{CatA}}\) is the arterial plasma concentration of norepinephrine or epinephrine (pg/ml).

The pulmonary fractional extraction of tritiated catecholamines (PulFx) was calculated as \( \frac{([\text{3H}\text{CatA}}\cdot \text{PulFx})}{([\text{3H}\text{CatPA}}\cdot (1 - \text{Hct})\) \cdot [\text{QLV}}\cdot (1 - \text{Hct})\)/body wt (14, 37).

Statistics. Physiological and catecholamine variables before and after desipramine were compared with repeated measures one-way analysis of variance, whereas norepinephrine and epinephrine kinetics were compared with the Student’s t-test (39). Results are reported as means ± SE, and \( P < 0.05 \) was considered significant.

### RESULTS

Hemodynamics, blood gas variables, and blood flows. Administration of desipramine was not associated with any significant changes in hemodynamics, systemic arterial blood gas variables, LV output, or the level of pulmonary blood flow derived from systemic sources (Table 1).

Endogenous and tritiated catecholamine plasma concentrations. Baseline endogenous systemic and pulmonary concentrations of either norepinephrine or epinephrine were not statistically different from one another, and no concentration changed significantly

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Values are means ± SE (n = 6). DMI, desipramine; Hct, hematocrit; MSABP, mean systemic arterial blood pressure; MPABP, mean pulmonary arterial blood pressure; LV output, left ventricular output; QPulSys, pulmonary blood flow derived from systemic sources.
after desipramine (Table 2). By contrast, under baseline conditions, the [3H]norepinephrine concentration in the pulmonary trunk exceeded that of the aorta by 163 ± 37 dpm/ml (P < 0.01), whereas the corresponding difference for [3H]epinephrine was 86 ± 9 dpm/ml (P < 0.001). Desipramine increased the pulmonary arterial and aortic concentrations of [3H]norepinephrine (both P < 0.001) and [3H]epinephrine (both P < 0.005) but abolished transpulmonary [3H]norepinephrine and [3H]epinephrine differences (Table 2).

Total body catecholamine clearance, fractional extraction, and spillover. Norepinephrine total body clearance decreased from 93 ± 8 to 46 ± 4 ml·min⁻¹·kg⁻¹ after desipramine (P < 0.001), and this was accompanied by a fall in the [3H]norepinephrine total body fractional extraction from 0.458 ± 0.057 to 0.215 ± 0.022 (P < 0.005; Fig. 2). Similarly, desipramine reduced epinephrine total body clearance from 82 ± 4 to 58 ± 6 ml·min⁻¹·kg⁻¹ (P < 0.01) in association with a reduction in [3H]epinephrine total body fractional extraction from 0.407 ± 0.044 to 0.284 ± 0.040 (P < 0.005; Fig. 2).

Comparison of desipramine-sensitive and desipramine-resistant fractional extractions indicated that neuronal uptake contributed 52 ± 3% of total body [3H]norepinephrine but only 31 ± 5% of total body [3H]epinephrine removal (P < 0.01). Furthermore, comparison of the reductions in the fraction extraction of [3H]norepinephrine (0.243 ± 0.042) and [3H]epinephrine (0.123 ± 0.022) indicated that total body desipramine-sensitive uptake of norepinephrine was twice as efficient as for epinephrine (P < 0.01).

In addition to the reduction in catecholamine clearance, desipramine decreased norepinephrine total body spillover from 188 ± 29 to 82 ± 16 ng·min⁻¹·kg⁻¹ (P < 0.005) and epinephrine total body spillover from 22.7 ± 2.7 to 13.8 ± 1.6 ng·min⁻¹·kg⁻¹ (P < 0.05; Fig 3).

Pulmonary catecholamine clearance and fractional extraction. The baseline pulmonary fractional extraction of [3H]norepinephrine was 0.133 ± 0.026, which constituted 35 ± 10% of total body [3H]norepinephrine extraction, whereas the pulmonary fractional extraction of [3H]epinephrine was 0.057 ± 0.007, which accounted for 15 ± 2% of total body epinephrine clearance. Desipramine reduced the pulmonary fractional extraction of both [3H]norepinephrine (P = 0.005) and [3H]epinephrine (P < 0.02) to undetectable levels (Fig. 4). Moreover, comparison of pre- and post-blockade fractional extractions indicated that [3H]norepinephrine was extracted 2.3-fold more efficiently than [3H]epinephrine by desipramine-sensitive removal processes in the lungs.

Pulmonary catecholamine spillover. Under baseline conditions, the specific activity of norepinephrine fell...
by 19.8 ± 5.7% (P < 0.02) and that of epinephrine by 7.2 ± 2.7% (P < 0.05) between the pulmonary trunk and aorta, indicative of a dilution of infused $^3$H-labeled catecholamines by endogenous catecholamines released from the lungs. However, desipramine reduced the transpulmonary difference in specific activity for norepinephrine (P < 0.02) and epinephrine (P < 0.03) to levels that were not significantly different from zero (Fig. 5).

Under baseline conditions, calculated pulmonary norepinephrine spillover was 79 ± 26 ng·min$^{-1}$·kg$^{-1}$, which constituted 47 ± 13% of total body norepinephrine spillover, whereas pulmonary epinephrine spillover was 3.8 ± 1.0 ng·min$^{-1}$·kg$^{-1}$, which accounted for 19 ± 7% of total body epinephrine spillover. However, desipramine administration was associated with a fall in both pulmonary norepinephrine (P < 0.03) and epinephrine spillovers (P < 0.05) to levels that were not statistically different from zero (Fig. 6).

**DISCUSSION**

This study has employed isotope dilution methodology to examine the effects of desipramine on pulmonary and total body clearance and spillover of norepinephrine and epinephrine in the immediate newborn period. To characterize catecholamine kinetics after birth in the absence of anesthesia and during spontaneous respiration, the study was performed in lambs that had been delivered by cesarean section close to term after adequate recovery from implantation of vascular catheters at prior in utero surgery. Previous work from this laboratory (35–38) has shown that such lambs undergo physiological changes typically associated with birth, including increases in arterial oxygenation, heart rate, systemic blood pressure, pulmonary blood flow, and circulating catecholamines, as well as reductions in pulmonary arterial blood pressure (2, 7, 8, 34). Further-
that of the adult and that the lower total body catecholamnergicneural uptake processes in the newborn was on a par with

In adult lungs, norepinephrine and epinephrine removal occurs via a transporter situated within the endothelial cells of the pulmonary microvasculature (6, 31). However, despite its location at an extraneuronal site, this transporter is not only inhibited by specific inhibitors of neuronal catecholamine uptake such as desipramine (6, 14) but also has an amino acid sequence identical to the neuronal catecholamine transporter (5). Two findings of the present study point to a close functional similarity between the catecholamine transporter in the newborn and adult lungs. First, in accord with the two- to fourfold difference seen in adult lungs (14, 19), pulmonary norepinephrine clearance in newborn lambs was 2.3-fold more efficient than for epinephrine. Second, as in adult dogs (14), desipramine reduced pulmonary \([^{3}H]\)norepinephrine and \([^{3}H]\)epinephrine extractions in newborn lambs to undetectable levels (Fig. 4). Collectively, these results suggest that, in contrast to the major roles of both neuronal and extraneuronal uptake processes in the systemic circulation (10, 12, 13, 15, 19–21), removal of circulating catecholamines by the lungs occurs primarily via the neuronal-like uptake mechanism located within the pulmonary microvasculature (6, 31). Although the basis for this difference is not fully understood at present, a likely contributory factor is the differing spatial arrangement of uptake mechanisms at these two sites, in that the pulmonary catecholamine transporter resides on the diffusional endothelial surface (31), whereas catecholamines in systemic tissues are exposed to extraneuronal uptake mechanisms en route to the neuronal transporter situated on perivascular and parenchymal sympathetic elements (17).

In addition to its inhibitory effect on neuronal uptake processes, desipramine also acts centrally to reduce sympathetic outflow (15), an action accompanied by a marked reduction in sympathetic nerve activity to organs such as skeletal muscle (18) and the kidney (15, 41). As most of the norepinephrine released by sympathetic nerves is recaptured, an effect of desipramine on neuronal uptake alone would increase the norepinephrine concentration at the neuroeffector junction and thereby result in a greater spillover of norepinephrine into plasma (17). However, norepinephrine spillover in normal adult humans and animals is either unchanged (14, 15, 20, 41) or reduced by 13–36% after desipramine (18, 28, 40), indicating that the two actions of this compound either counteract one another or slightly favor central sympathoinhibition. In contrast, desipramine caused a 56% reduction in the total body spillover of norepinephrine in newborn lambs (Fig. 3), an observation that not only suggests that this agent exerted a predominant central sympathoinhibitory effect in the newborn, but also supports an important role for

In accord with the higher affinity of norepinephrine as a substrate for neuronal uptake observed in the adult (10, 14, 19), desipramine also produced a greater reduction in norepinephrine total body removal relative to that of epinephrine in newborn lambs (Fig. 2). Moreover, the observation that whole body clearance of circulating \([^{3}H]\)norepinephrine in the present study was reduced by 51%, compared with 20–42% in the adult (10, 14, 18, 19, 40), and circulating \([^{3}H]\)epinephrine by 29%, compared with no change (10) or a reduction of 13–19% (10, 14) in the adult, is consistent with a greater dependency of neonatal total body catecholamine clearance on desipramine-sensitive mechanisms. A likely basis for this phenomenon is apparent from examination of catecholamine total body fractional extraction data. Thus, although the total body fractional extraction of \([^{3}H]\)norepinephrine (0.46) and \([^{3}H]\)epinephrine (0.41) observed in newborn lambs was substantially lower than the corresponding ranges of 0.66–0.71 (14, 19, 21) and 0.65–0.72 (14, 21) reported in adult humans and experimental animals, the desipramine-induced fall in total body norepinephrine fractional extraction in newborn lambs (0.245) was similar to the adult range of 0.219–0.254 (14, 19), whereas the reduction in total body epinephrine fractional extraction (0.123) was even greater than the adult range of 0.061–0.086 (14, 19). These results imply that, despite the presence of incompletely developed sympathetic innervation (27), the maturity of catecholamine neuronal uptake processes in the newborn was on a par with
central mechanisms in the increased sympathetic activation occurring at birth (33).

It is unlikely that norepinephrine arising from the newborn lungs was derived from a source other than sympathetic nerves. Specifically, recent studies in isolated rat lungs indicate that norepinephrine taken up into pulmonary endothelial cells is primarily metabolized to O-methylated compounds by catechol O-methyltransferase (COMT), an enzyme that becomes half saturated at a norepinephrine concentration of 9.8 nmol/l (4). Furthermore, saturation of pulmonary COMT results in the accumulation (4) and subsequent efflux of unchanged norepinephrine from pulmonary endothelial cells (42). However, although our baseline pulmonary arterial norepinephrine concentration of 1,888 pg/ml was equivalent to 11.2 nmol/l, it is unlikely that the foregoing mechanism made a significant contribution to pulmonary norepinephrine release in newborn lambs, because blockade of the pulmonary catecholamine transporter would then have increased norepinephrine efflux (42) and therefore spillover, whereas desipramine reduced norepinephrine spillover to near-zero levels in our study (Fig. 6).

Although desipramine does not alter total body epinephrine release in the adult (14, 20), this compound reduced epinephrine total body release by 39% in newborn lambs of the present study (Fig. 6). As with our norepinephrine data, this suggests that any increased epinephrine release into the circulation related to blockade of the pulmonary catecholamine transporter was outweighed by the central sympathoinhibitory effects of desipramine (15, 41). Furthermore, the finding that about two-fifths of the reduction in total body epinephrine was related to a marked fall in pulmonary epinephrine efflux extends our previous finding that the newborn lungs are a major extraadrenal site of epinephrine release (37) by implying that such release can be modulated by sympathetic outflow from the central nervous system.

An important issue that is still to be fully resolved relates to the precise origin of the epinephrine released from newborn lungs. The most straightforward explanation, which is consistent with the concurrent reduction in norepinephrine and epinephrine spillovers to undetectable levels after desipramine (Fig. 6), was that epinephrine was co-released with norepinephrine from pulmonary sympathetic nerve endings. One possible source of this epinephrine was a loading of pulmonary neuronal epinephrine stores via uptake from the circulation (29) occurring in association with the perinatal surge in plasma epinephrine concentration (33). However, the demonstration of the epinephrine-synthesizing enzyme phenylethanolamine N-methyltransferase in the developing lung and the increased activity of this enzyme in the initial days after birth (32) as well as our previous kinetic analysis (37) suggests that epinephrine is also synthesized within newborn lungs. Evidence from adult rats of lung epinephrine synthesis within an extraneuronal site (25) points to the neuroendocrine cell, which occurs in abundance in newborn lungs (23), as a likely candidate for such synthesis. Importantly, extraneuronal synthesis is not necessarily incompatible with neuronal release because data from the heart and skeletal muscle (26) suggest that epinephrine synthesized in an extraneuronal location may be sequestered into sympathetic neurons.

Perspectives

The results of this study suggest that the removal and release of norepinephrine and epinephrine by the newborn lungs are mediated by desipramine-sensitive processes and that these pulmonary effects account for a major part of the associated reduction in total body norepinephrine and epinephrine clearance and release. Understanding the factors that regulate postnatal catecholamine kinetics in the lungs, particularly that of epinephrine, has both physiological and clinical relevance because adrenergic mechanisms are known to play a central role in the pulmonary vascular and respiratory adjustments that occur after birth (33). However, the contribution of locally released norepinephrine and epinephrine to these adjustments is yet to be fully elucidated, as is the nature of disturbances in these mechanisms that may occur in conditions such as fetal growth restriction, preterm delivery, and persistent pulmonary hypertension of the newborn.

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