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Functional Ontogeny of Pulmonary Vascular DA_1 Dopamine Receptors in the Isolated Perfused Rabbit Lung

MARK J. POLAK AND DAVID A. TAYLOR

Departments of Pediatrics [M.J.P.] and Pharmacology/Toxicology [D.A.T.], West Virginia University School of Medicine, Morgantown, West Virginia 26506-9214

ABSTRACT. Using an *in situ* isolated salt-perfused rabbit lung preparation, we investigated the functional ontogeny of pulmonary vascular dopamine receptors. In rabbits from 1 to 23 d of age, we measured pulmonary vascular vasodilatory responses to the peripheral vascular dopamine receptor (DA_1) agonist, fenoldopam, and sodium nitroprusside during prostaglandin $F_{2\alpha}$-induced pulmonary vasoconstriction. In separate experiments, the lungs were pretreated with the DA_1 receptor blocker, SCH 23390, before prostaglandin $F_{2\alpha}$, fenoldopam, and sodium nitroprusside. Lungs from rabbits at one of 6 age groups (n = 6–8 per group) were ventilated and perfused. After a stabilization period, prostaglandin $F_{2\alpha}$ was infused into the pulmonary inflow catheter in a concentration range to yield a sustained rise in mean pulmonary artery pressure (4.9 ± 0.2 mm Hg). Fenoldopam was injected into the pulmonary artery at doses of 0.01, 0.1, 1.0, and 10 μg/g after a recovery period, sodium nitroprusside (0.2 μg/g) was injected into the pulmonary artery, and the resultant changes in vascular pressure were recorded. Across all age groups, with and without DA_1 receptor blockade, sodium nitroprusside–induced vasodilation was similar (−2.7 ± 0.2 mm Hg) and was considered reference vasodilation. The fenoldopam vasodilation response was considered a percentage of the sodium nitroprusside reference. Response to fenoldopam varied significantly ($p < 0.05$ by analysis of variance) across the six age groups, with a maximum at 3–5 d of age. Pretreatment with SCH 23390, a selective DA_1-blocking agent, significantly attenuated fenoldopam vasodilation in all but the youngest animals (age 0–2 d), in which no blockade effect was noted. We conclude that there are significant age-related changes in the vascular responses to fenoldopam. We speculate that endogenous dopamine and vascular dopamine receptors may play a role in mediating changes in the transitional, pulmonary circulation. (*Pediatr Res* 35: 228–232, 1994)

Abbreviations

DA_1, peripheral vascular dopamine receptor
ANOVA, analysis of variance
$PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$

Endogenous dopamine interacts with a family of receptors within the CNS and peripherally within various organs and vascular beds. Dopamine–dopamine receptor interactions have a role in endocrine integrity, movement, behavior, renal function, and hemodynamics (1, 2). Recent studies have suggested that dopamine and peripheral, postsynaptic vascular, and renal tubule dopamine receptors (DA_1) are important in the modulation of systemic blood pressure and renal function in the fetus and newborn (2–6). We wondered whether dopamine receptor activity plays a role in neonatal pulmonary vascular reactivity.

In these studies, we have investigated the functional maturation of DA_1-type receptors in the pulmonary vasculature of rabbits. We approached the evaluation of DA_1 receptor function in newborns by using the DA_1 receptor agonist-antagonist pair of fenoldopam and SCH 23390 in a preconstricted, isolated perfused rabbit lung model. This agonist-antagonist pair provides a powerful tool for delineating functional activity of dopamine receptors (6–8). Our data show changes in vascular dopamine receptor responsiveness in neonatal rabbits occurring during the first 3 wk of life. These changes may play a role in modulation of pulmonary hemodynamics in the newborn.

MATERIALS AND METHODS

These experiments were approved by the Animal Care and Use Committee at West Virginia University. Pregnant, New Zealand White rabbit does delivered spontaneously at term (31 d gestation). The pups were nested with the mother and randomly assigned to a perfusion group. Rabbits were divided on the basis of age into six perfusion groups, which are detailed in Table 1.

On the day of perfusion, the rabbit pup was removed from the nest, taken to the laboratory, and weighed. The animal was instrumented for perfusion as follows. The rabbit pup was anesthetized with pentobarbitol (50 μg/g body weight) injected intraperitoneally. A tracheostomy was performed and mechanical ventilation begun (O_2 = 0.21, CO_2 = 0.05, N_2 = 0.74, tidal volume = 1.2 mL/100 g, rate = 30 breaths/min). The heart and lungs were exposed via a median sternotomy, heparin (1 U/g body weight) was injected into the right ventricle, and a ligature was placed loosely around the pulmonic and aortic trunks. A perfusion cannula was inserted into the main pulmonary artery through a small incision in the right ventricular outflow tract. The ligature was tightened around both the pulmonary artery and aorta and an infusion begun with Earl's Balanced Salt Solution with 21 mM sodium bicarbonate and 3% bovine albumin added. The pH was adjusted to 7.40. The tip of the left ventricle was excised and a second cannula introduced into the left atrium and fixed into position with a ligature around both ventricles. The ductus arteriosus was identified and, if present, ligated with a fine suture ligature (between 3 and 5 d of age, the ductus arteriosus was noted to constrict).

The perfusate was pumped from a syringe reservoir, at constant

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Correspondence: Mark J. Polak, M.D., Department of Pediatrics, Box 9214 R. C. Byrd Health Science Center, North, West Virginia University School of Medicine, Morgantown, WV 26506-9214.
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Table 1. *Stability data for fenoldopan and fenoldopam + SCH 23390 dose-response experiments in isolated perfused rabbit lung model**

Age group (d)	*n*	Age (d)	Weight (g)	Flow (mL/kg·min^{-1})	Baseline PAP (mm Hg)	$PGF_{2\alpha}$ vasoconstriction (ΔPAP from baseline, mm Hg)	Wet/dry ratio
No blockade							
1 (0–2)	6	1.2 ± 0.2	66.7 ± 5.4	52.9 ± 1.3	13.6 ± 2.0	6.0 ± 0.6	3.7 ± 0.2
2 (3–5)	8	3.3 ± 0.2	92.6 ± 5.0	53.2 ± 0.9	17.9 ± 1.2	4.7 ± 0.3	3.8 ± 0.2
3 (6–8)	6	7.0 ± 0.1	157.7 ± 8.4	50.9 ± 0.5	16.7 ± 1.7	5.1 ± 0.5	4.2 ± 0.4
4 (9–12)	6	10.0 ± 0.2	230.0 ± 11.0	52.6 ± 0.6	19.9 ± 1.7	4.8 ± 0.6	4.1 ± 0.2
5 (13–17)	6	14.2 ± 0.2	250.0 ± 35.8	53.2 ± 1.1	15.7 ± 1.2	4.3 ± 0.3	4.4 ± 0.2
6 (18–23)	8	22.0 ± 0.6	319.0 ± 37.9	53.3 ± 1.1	19.0 ± 1.8	5.1 ± 0.4	4.4 ± 0.2
SCH 23390 (0.01 μg/g·min^{-1})							
1 (0–2)	3	2.0 ± 0.2	64.7 ± 5.9	53.4 ± 1.0	15.7 ± 0.7	6.1 ± 0.1	4.0 ± 0.3
2 (3–5)	4	4.0 ± 1.1	90.8 ± 5.0	52.2 ± 0.8	17.7 ± 0.7	5.2 ± 0.4	3.9 ± 0.3
3 (6–8)	3	6.5 ± 0.3	127.7 ± 17.7	52.8 ± 1.5	17.3 ± 1.4	5.8 ± 0.2	4.1 ± 0.4
4 (9–12)	3	11.0 ± 1.0	190.0 ± 6.0	51.4 ± 0.9	16.3 ± 0.8	4.5 ± 0.3	4.0 ± 0.2
5 (13–17)	4	15.0 ± 0.6	273.0 ± 43.8	52.0 ± 0.7	16.5 ± 1.0	5.3 ± 0.4	3.9 ± 0.5
6 (18–23)	4	20.0 ± 0.8	300.0 ± 29.0	54.0 ± 0.4	15.0 ± 1.0	5.8 ± 0.4	4.2 ± 0.3

* PAP, pulmonary artery pressure.

flow rate, through a heat exchanger (temperature = 37°C) and into the pulmonary artery, where it is circulated through the lungs and returned to the reservoir via the left atrial catheter. Mean pulmonary artery pressure and mean left atrial pressure (mm Hg) were continuously measured by pressure transducers and monitored on a physiologic recorder.

The experimental protocols were designed to investigate the dose-response characteristics of selective DA_1 receptor stimulation with fenoldopam on the pulmonary vascular bed during elevated pulmonary artery pressure as a function of age (Fig. 1). Fenoldopam mesylate is a benzapine compound developed as an antihypertensive agent. It is a highly selective DA_1 receptor agonist (9, 10). Because tachyphylaxis is generally not noted with fenoldopam (11), a sequential dose-response protocol was developed. The fenoldopam doses were chosen on the basis of previous work from our laboratory (6–8) and pilot studies in rabbits.

As a test for DA_1 receptor selectivity, the fenoldopam dose-response experiments were repeated in the presence of the highly selective DA_1 receptor blocker, SCH 23390 (12–14). This drug has no known cross-reactivity to DA_2-, α-, or β-adrenergic, histaminergic, serotonergic, or cholinergic receptors. From our previous experience, SCH 23390 infused at 0.01 μg/g·min^{-1} does not alter baseline pressure or other lung perfusion characteristics, yet significantly blocks the fenoldopam effect (6–8).

Finally, as a measure of age-independent vasodilation, with and without DA_1 blockade, sodium nitroprusside (0.2 μg/g body weight) was used. Sodium nitroprusside causes endothelium-independent vasodilation via stimulation of soluble guanylate cyclase within the vascular smooth muscle. As a result, the vasodilator response to sodium nitroprusside does not vary with age (15, 16).

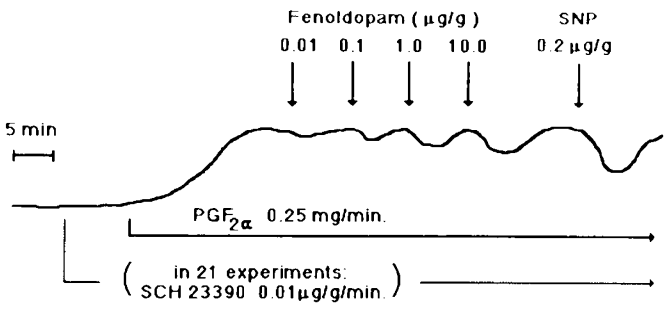

Fig. 1. Outline of experimental protocols. A total of 61 perfusion experiments were completed on 61 separate rabbits. *SNP*, sodium nitroprusside.

A 10- to 15-min stabilization period began each experiment. Flow was set to greater than 0.050 mL/g·min^{-1}, and left atrial pressure was adjusted to 1–2 mm Hg. A solution of $PGF_{2\alpha}$ (0.25 μg/g·min^{-1}) was infused into the pulmonary artery to elevate the mean pulmonary artery pressure with no alteration in mean left atrial pressure. Fenoldopam, in doses of 0.01, 0.1, 1.0, and 10.0 μg/g of rabbit body weight, was serially injected into the pulmonary artery, and the maximum changes in pulmonary vascular pressure (mm Hg) were recorded. After an additional 10 min, sodium nitroprusside (0.2 μg/g) was injected into the pulmonary artery, and the resultant change in pulmonary artery pressure (mm Hg) recorded. In 21 separate experiments, a solution of the selective DA_1 blocker SCH 23390 was infused at 0.01 μg/g·min^{-1} into the pulmonary artery before the $PGF_{2\alpha}$ was infused. Fenoldopam at doses of 0.1 and 1.0 μg/g was used in these experiments. At the end of all experiments, the lungs were removed, weighed, dried in a drying oven, and reweighed. Wet-to-dry lung weight ratios were calculated as a determination of lung edema. From our previous experience, a wet/dry ratio of 6.0 or less is indicative of little or no edema formation (6–8) and, in general, a good perfusion.

For all experiments, the sodium nitroprusside–induced vasodilation was considered the reference vasodilation. This response was given an arbitrary value of 100% vasodilation. The degree of vasodilation attained by fenoldopam was subsequently represented as a percentage of the nitroprusside reference. The overall data were analyzed by single-factor ANOVA with age group as the independent variable and percent change in pulmonary pressure as the dependent variable. Significant differences among different age groups at each dose of fenoldopam were determined by the Fisher's protected least squares difference test and the Scheffe *F* test. Comparisons of fenoldopam vasodilation with and without DA_1 blockade within each age group were made by single-factor ANOVA. All data are presented as mean ± SEM.

RESULTS

A total of 61 perfusion experiments were performed on the six age groups. In all age groups, with and without DA_1 blockade, baseline pulmonary artery pressure ranged from 13.6 to 19.9 mm Hg, $PGF_{2\alpha}$ caused an increase in pulmonary artery pressure of 4.5 to 6.0 mm Hg from baseline, nitroprusside caused a 2.5 to 3.3 mm Hg decrease in pulmonary artery pressure from $PGF_{2\alpha}$-elevated state, and wet to dry ratios were similar (Table 1).

Fenoldopam-induced vasodilation as a function of age. As previously noted, the degree of vasodilation attained by fenol-

dopam in each age group is represented as a percentage of the nitroprusside reference. The vascular responses to fenoldopam as a function of age are detailed in Figure 2. A vasodilatory response to fenoldopam is noted even in the youngest age group (group 1). The dose-response curve then shifts to the left, with the maximum vasodilatory responses to fenoldopam noted in age group 2. Fenoldopam vasodilation at doses of 0.1 and 1.0 μg/g in age group 2 was significantly higher than in all other age groups. The dose-response curve then shifts rightward over the following 2 wk and remains at these levels to the weanling age.

Fenoldopam vasodilation after DA_1 blockade with SCH 23390. To investigate the degree of DA_1 receptor specificity with the fenoldopam-induced vasodilation, the experiments were repeated in the presence of the selective DA_1-blocking agent SCH 23390. As can be noted in Figure 3, treatment with this dopamine receptor antagonist significantly attenuates the vasodilatory responses to fenoldopam in all age groups except group 1, in which no effect of DA_1 blockade was noted.

DISCUSSION

The isolated perfused lung has proven to be a useful model for detailing the effects of dopamine receptor manipulation on the pulmonary vasculature (7, 8). In these present experiments, we have reexamined the effects of DA_1 stimulation on the preconstricted pulmonary vascular bed of rabbits as a function of age, newborn to weanling. We have shown that there are distinct differences in DA_1 receptor responsiveness and receptor selectivity that change with the age of the animals.

Pulmonary vascular dynamics are complex in the newborn mammal, because there are major transitions from fetal to newborn circulations and ultimately to the development of adult blood flow patterns. Control of pulmonary vascular tone in the fetus and the transition to the newborn are dictated by many interacting mechanisms, including environmental factors (pH, hypoxia, *etc*), as well as the production and metabolism of a variety of vasoactive compounds within the pulmonary vessels including bradykinin and other vasoactive peptides, products of arachidonic acid metabolism, and endothelium-derived factors (endothelium-derived relaxing factor, endothelin) (17, 18). Autonomic control of vascular tone in terms of sympathetic input seems to have a limited role in the fetal and transitional circulation because innervation has been classically thought to be incomplete at birth (19, 20).

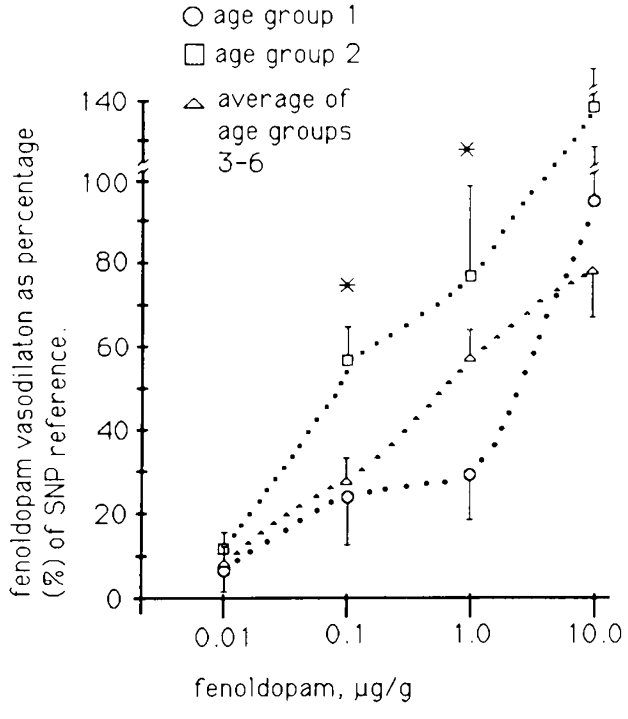

Fig. 2. Dose-response curves for fenoldopam vasodilation at different ages. Note that age groups 3 through 6 have been averaged and are represented by △. *SNP*, sodium nitroprusside. *, Significant difference of fenoldopam vasodilation in age group 2 compared with age groups 1, 3, 4, 5, and 6 as determined by ANOVA. The α level of significance is $p < 0.05$.

Recent data suggest that peripheral dopaminergic activity may also be important in modulating the hemodynamics of the fetus and newborn. In the fetal lamb, endogenous dopamine plays an important role in control of renal function, primarily by affecting sodium excretion. These dopamine-DA_1 receptor interactions occur at the tubular level, in response to dopamine produced locally (2–5). In the fetal and neonatal lamb, blockade of peripheral DA_1 receptors with SCH 23390 causes significant alterations in heart rate, cardiac output, systemic and pulmonary artery pressure, and systemic and pulmonary vascular resistance (5, 6). These data suggest that endogenous dopamine has numerous physiologic actions in the fetus and newborn. The renal tubule DA_1 receptor activation is involved in control of vascular volume status, whereas vascular DA_1 receptor occupation affects multiple vascular systems of these animals. These vascular dopamine receptors not only have an affinity for dopamine receptor agonists such as fenoldopam, but also can effect vascular hemodynamics and seem to be maintained in a chronically active state, presumably by endogenous dopamine (5, 6, 11, 21).

At birth and for the first 2 d of life, there is a dose-dependent vasodilatory response to fenoldopam. This vasodilatory response, however, is not necessarily the result of DA_1 receptor activation, as demonstrated by the failure to reach a dose-response saturation point typical of a drug-receptor interaction (Fig. 2) (22). Furthermore, SCH 23390 failed to block the fenoldopam-induced vasodilation, supporting the idea of a vasodilating effect mediated by an atypical DA_1 receptor at best (Fig. 3). Postnatal maturation of dopamine receptor responsiveness occurs at different time courses for different circulations (23, 24); therefore, the functional ontogeny of pulmonary vascular dopamine receptors may not necessarily parallel the patterns noted in the renal tubules and vascular beds of other organ systems. From our data, it appears that maturation of pulmonary dopamine (DA_1) receptors does differ from that previously noted in the fetal and newborn kidney. The observations of highly uncharacteristic effects of fenoldopam and SCH 23390 in age group 1 may be the result of multiple factors including altered affinity for binding of receptors for both agonists and/or antagonists, differences in receptor density, and differences in the efficiency with which the agonists are coupled to their transduction mechanisms, adenylate cyclase and phospholipase C. Considering all these factors, the data suggest that endogenous dopamine-dopamine receptor interactions during this early period do not play a major role in control of pulmonary vascular tone.

After this period (group 1; 0–2 d) of fenoldopam and SCH 23390 interactions that might not be DA_1 receptor-specific responses, there are rather dramatic changes, in both the vascular responsiveness to fenoldopam and the DA_1 receptor-blocking activity of SCH 23390 that occur between 3 and 5 d of age. Fenoldopam-induced vasodilation, measured as a dose-response curve, in age group 2 is shifted to the left compared with both the younger (0–2 d) and older (6–23 d) animals. In contrast to group 1, a saturation point in the dose-response curve is reached (fenoldopam vasodilations at 1.0 and 10.0 μg/g are not significantly different by repeated measures ANOVA). Also, in contrast with the earliest age group, the vasodilatory responses in this age group are significantly blunted by SCH 23390 (Fig. 3). Taken together, these findings suggest that during this time period the enhanced vasodilatory action of fenoldopam is caused by stimulation of vascular DA_1 receptors. This increase in the pulmonary vascular responsiveness to DA_1 receptor manipulation may reflect changes occurring with maturation of autonomic innerva-

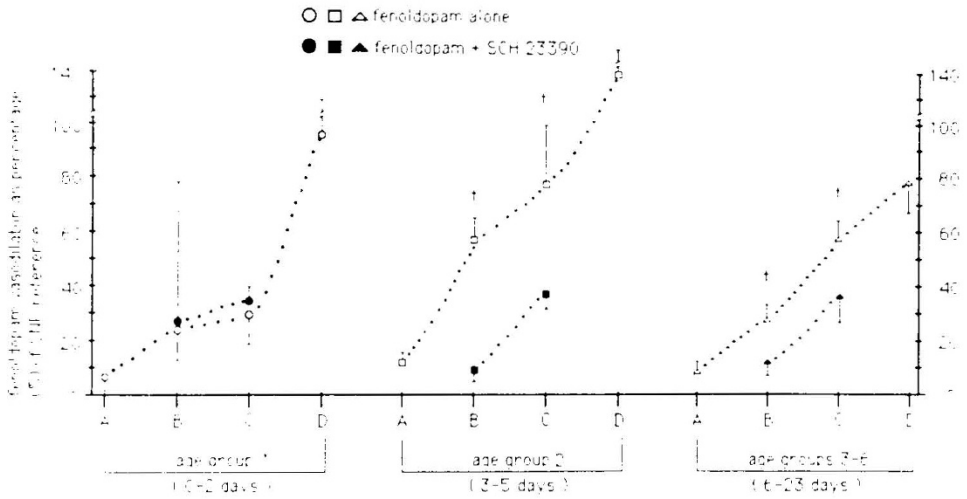

Fig. 3. The effect of DA_1 blockade (SCH 23390) on the dose-response curves for fenoldopam vasodilation. As in Figure 2, age groups 3 through 6 have been averaged and are represented by △ and ▲. Letter notations on the x axis indicate fenoldopam dose (μg/g body weight): *A*, 0.01; *B*, 0.1; *C*, 1.0; and *D*, 10.0. †, Significant difference, DA_1 blockade *vs* no blockade by ANOVA. The α level of significance is $p < 0.05$.

tion. One explanation may involve the ontogeny of vascular tone control mechanisms. In the fetus, vascular tone is largely mediated by locally released factors. However, a considerable degree of autonomic input and control (involving adrenergic nervous input) occurs after birth. Such age-related changes in the sensitivity of cardiovascular tissues to receptor activation have been previously noted (25). These sensitivity changes are thought to represent the appearance of neuroeffector transmission and may be related to an effect of functional innervation or the removal of depressant mechanisms associated with ontogenesis.

If the changes in DA_1 receptor responsiveness do indeed reflect developing innervation, then we may speculate that sympathetic dopaminergic nerves are also important in the transitional pulmonary circulation. A role for the sympathetic nervous system in control of hemodynamics occurring before the time frame classically described (19, 20) has been shown to exist in the kidney, where sympathetic innervation is well developed by the time of birth so as to participate in the renovascular changes occurring at birth (26, 27). Previous studies that detail delayed innervation in the lung did not examine the rather short period of increased activity reported in our study by increased receptor responsiveness. More importantly, however, most work to this point has been focused on developing adrenergic rather than dopaminergic innervation.

Between age groups 3 and 6, the fenoldopam dose-response curve shifts back toward the right, where it remains through the weanling age. The dose-responsive curves for these age groups (averaged in Fig. 2) have the sigmoid characteristics of a normal drug-receptor interaction (22), suggesting a similar fenoldopam–DA_1 receptor interaction. The DA_1 receptor selectivity, as measured by significant SCH 23390 blockade (Fig. 3), is also maintained.

These studies indicate that there are significant age-related changes in the vascular responses to fenoldopam and SCH 23390. We believe that these data reflect maturation of DA_1 receptors in the pulmonary vasculature. These changes in responsiveness to vascular DA_1-type dopamine receptor activation may reflect developing dopaminergic innervation patterns. Dopaminergic input is one of the many factors that are likely to be important in the control of the transitional circulation. A similar period of increased DA_1 responsiveness in the human neonate may have clinical significance.

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Erratum

In the article "Brain Vasoactive Effects of Phenobarbital during Hypertension and Hypoxia in Newborn Pigs" (Pediatric Research 32:103–106, 1992), an error was made in the equation on page 104. The correct equation should read:

$$\text{CBF}\ (\text{mL}\cdot\text{min}^{-1}\cdot 100\ \text{g}^{-1}) = \text{counts}\cdot\text{min}^{-1}\cdot 100\ \text{g}^{-1}\ \text{of brain}\cdot\frac{\text{reference withdrawal rate/counts}\cdot\text{min}^{-1}}{\text{in reference blood}}$$

The authors regret this error.