Metabolic Responses Induced in Neonatal Swine by Norepinephrine, Epinephrine, and Isoproterenol (37350)

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The elevation of catecholamines or their metabolites in the plasma or urine of young swine exposed to cold, starvation, heat or electrical shock demonstrates that the sympathetic nervous system of this species is activated by stress (1–3). Furthermore, adrenal gland tyrosine hydroxylase activity is enhanced and catecholamine content is diminished in neonatal swine which are frequently handled (4). Certain swine are more responsive to stress than others and may succumb from a condition known as the "porcine stress syndrome." Topel (2) has recently suggested that the adrenergic β receptors of these "stress-susceptible" pigs are more easily activated by catecholamines than receptors of "stress-resistant" swine. Little is known about the metabolic effects of catecholamines in swine in spite of the evidence of adrenergic involvement in stress in this species. Particularly, we could find no reports of studies comparing the metabolic actions of the three common catecholamines, epinephrine, norepinephrine, and isoproterenol, in swine. The following report describes the results obtained when these agents were administered to newborn and 7-day-old piglets. Information of this type is requisite to an understanding of the response of the neonate to stress during the early perinatal period.

Methods. The piglets used in this study were obtained from Duroc sows crossbred to Chester White boars. The animals were born in temperature-controlled facilities maintained at 23–24° with additional warmth provided by lamps. Newborn piglets were allowed one hour to nurse before use, while 7-day-old animals were taken within an hour of feeding. The newborn animals were kept in the laboratory at 34–35°, while 7-day-old piglets were maintained at 27–30°.

Although anesthesia may alter the metabolic state of the animal, handling is particularly stressful to swine, and the following procedures were, therefore, employed to minimize both variables. A polyethylene catheter (PE 50) was inserted through a needle into the peritoneal cavity and was taped to the skin of the animal. The catheter length was such that an injection could be given without disturbing the animal. The piglet, with the catheter inserted, was placed in a warm, ventilated ice chest with a plexiglass viewing window in the lid and was allowed to adapt to its environment for 30 min. The catecholamine or 0.9% NaCl solution was injected through the catheter without disturbing the animal. Ten min after the injection, halothane was introduced into the ice chest via inlet ports by pumping room air through a Fluotec 3™ vaporizer with a small laboratory pressure/vacuum pump. The animal, when visibly anesthetized, was removed from the chamber (about 5 min), the chest was rapidly opened along a midventral line and a blood sample was withdrawn from the heart into a chilled, heparin-primed syringe. A portion of liver was rapidly excised, immediately frozen in liquid N_2 and stored at −20° until it was analyzed for glycogen phosphorylase activity.

An aliquot of the blood sample was rapidly deproteinized with 8% perchloric acid, and the supernate was used for determining lactic acid (5). Glucose was measured in plasma with an automated glucose oxidase method (6). Plasma nonesterified fatty acids were extracted (7) and titrated in a one-phase system with tetrabutyl ammonium hydroxide

using phenol red as an indicator (8). Liver glycogen phosphorylase activity was assayed as previously described (9).

The 15-min sampling period was used because preliminary experiments with newborn piglets indicated that the epinephrine-induced responses were not enhanced 30 min after catecholamine administration. The catecholamines were freshly prepared in 0.9% NaCl from hydrochloride salts.

Results. The metabolic actions induced by the intraperitoneal administration of epinephrine (E), norepinephrine (N) and isoproterenol (I) to 3-hr-old, newborn or 7-day-old piglets are summarized in Table I. These data were analyzed by an analysis of variance and significance was assessed from least significant differences. The standard errors were computed from the error mean squares obtained in the analysis of variance (10).

Plasma glucose was elevated in newborn and 7-day-old animals by the three catecholamines. The 125 μg/kg dose of N, E, or I elicited an equivalent degree of hyperglycemia in newborn animals. No greater response was obtained with 500 μg/kg of N than with 125 μg/kg, but the larger dose was more active than the smaller when E or I were administered to newborn piglets. The order of activity in 7-day-old animals treated with 125 μg/kg was I > E > N.

Although blood lactate was significantly ($p < 0.05$) elevated by some catecholamine treatments (newborn—N_{500}, E_{500}, I_{125}; 7 day—I_{125}), these changes were small compared to the 5-fold increases observed in mature rats treated with I, 200 μg/kg, ip (11).

Plasma nonesterified fatty acids (NEFA) were not significantly elevated by N, E, or

TABLE I. Metabolic Responses Induced in Neonatal Swine by Catecholamines.[a]

	Piglet age										
	3 Hr old							7 Days old			
		N, μg/kg		E, μg/kg		I, μg/kg					
Parameter	0.9% NaCl	125	500	125	500	125	500	0.9% NaCl	N, 125 μg/kg	E, 125 μg/kg	I, 125 μg/kg
No. of piglets	13	7	6	6	5	6	4	6	6	6	6
No. of litters	5	3	3	4	2	3	2	3	3	3	4
Body wt (kg)	1.31 ±.08[c]	1.34 ±.08	1.10 ±.10	1.27 ±.10	1.36 ±.12	1.33 ±.12	1.22 ±.14	1.78 ±.16	2.03 ±.08	1.70 ±.20	1.80 ±.21
Plasma glucose (mg/100 ml)	70 ±6[c]	97 ±8[b]	89 ±9[b]	104 ±9[b]	181 ±10[b]	117 ±9[b]	136 ±11[b]	99 ±9	149 ±9[b]	160 ±9[b]	179 ±9[b]
Blood lactate (mg/100 ml)	20 ±2	20 ±2	30 ±3[b]	22 ±3	32 ±3[b]	29 ±3[b]	19 ±3	23 ±4	24 ±4	29 ±4	36 ±4[b]
Plasma NEFA (μmole/liter)	275 ±27	277 ±36	219 ±43	260 ±39	219 ±43	327 ±39	351 ±48	340 ±88	459 ±88	630 ±88[b]	694 ±88[b]
Liver glycogen phosphorylase activity (μmole pi/hr/mg prot.)	3.2 ±0.4	4.7 ±0.6[b]	4.7 ±0.6[b]	7.3 ±0.6[b]	6.4 ±0.7[b]	8.0 ±0.6[b]	6.5 ±0.8[b]	2.5 ±0.4[b]	4.7 ±0.4	5.1 ±0.4[b]	5.6 ±0.4[b]

[a] Measured 15 min after catecholamine administration.

[b] Statistically different ($p < 0.05$) than 0.9% NaCl solution controls.

N = norepinephrine, E = epinephrine, and I = isoproterenol.

[c] Standard errors for body wt were calculated by standard procedures for each treatment group. Data from 3-hr-old animals were analyzed by a 2-way analysis of variance, while 7-day-old groups were evaluated with a 1-way analysis. The appropriate error mean square from each analysis was used to calculate the metabolic product standard errors.

I, 125 or 500 μg/kg administered to newborn piglets. NEFA levels were significantly ($p < 0.05$) elevated by 125 μg/kg of E and I, but not by N administered to 7-day-old animals. Liver glycogen phosphorylase was significantly ($p < 0.05$) activated by the three catecholamines administered to newborn and 7-day-old swine. The activation was as great after 125 μg/kg as after 500 μg/kg in the newborn animals.

Discussion. "Newborn" piglets were less responsive in this study than 7-day-old animals to the hyperglycemic actions of catecholamines, particularly norepinephrine. We have also observed that anesthetized, fed, newborn swine were less responsive to the hyperglycemic effects of intravenously administered epinephrine or norepinephrine than older animals (3). Persson *et al.* (12) demonstrated that norepinephrine infusions induced less increase in blood glucose in young (1–2 days old) than in older (5–12 days old) piglets.

Isoproterenol increased plasma glucose as much as epinephrine in the neonatal pig. This is similar to the cat and dog but differs from the fed rat, rabbit or man where isoproterenol elicits little hyperglycemia (13). Liver phosphorylase was also activated in the young swine by the three catecholamines. This differs from the rat where isoproterenol does not seem to activate liver phosphorylase or glycogenolysis *in vivo* or *in vitro* (13). Although studies with adrenergic blocking agents would be useful for confirmation, our data suggest that the sympathetic receptors responsible for liver glycogenolysis in the swine are of the classical, β adrenergic type.

Catecholamines, including the potent adrenergic β receptor agonist, isoproterenol, do not seem to activate lipolysis in the fed, newborn pig, although epinephrine and isoproterenol were quite active in 7-day-old animals. This supports, in part, the observations of Curtis and Rogler and Persson *et al.* that intravenous injections (14) or infusions (12) of norepinephrine induce little or no increases in plasma NEFA of 6 to 30-hr-old swine. Norepinephrine induced appreciable lipolysis in older animals (> 54 hr) in those studies. Norepinephrine in our experiments did not induce statistically significant lipolysis in 7-day-old piglets, although the plasma levels seemed elevated and a higher dose may have elicited a significant response.

Summary. Norepinephrine (N), epinephrine (E), and isoproterenol (I) increased plasma glucose in fed, newborn, and 7-day-old swine when administered by the intraperitoneal route. Liver glycogen phosphorylase was activated by the three catecholamines in newborn and 7-day-old animals. The three catecholamines did not increase plasma NEFA levels in newborn swine, although E and I induced significant lipolysis in 7-day-old animals. Norepinephrine did not induce statistically significant increases in plasma NEFA levels of the older piglets, although there was a trend toward enhanced lipolysis in this group.

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