猪的精氨酸营养与繁殖性能

Arginine Nutrition and Reproductive Performance in Swine

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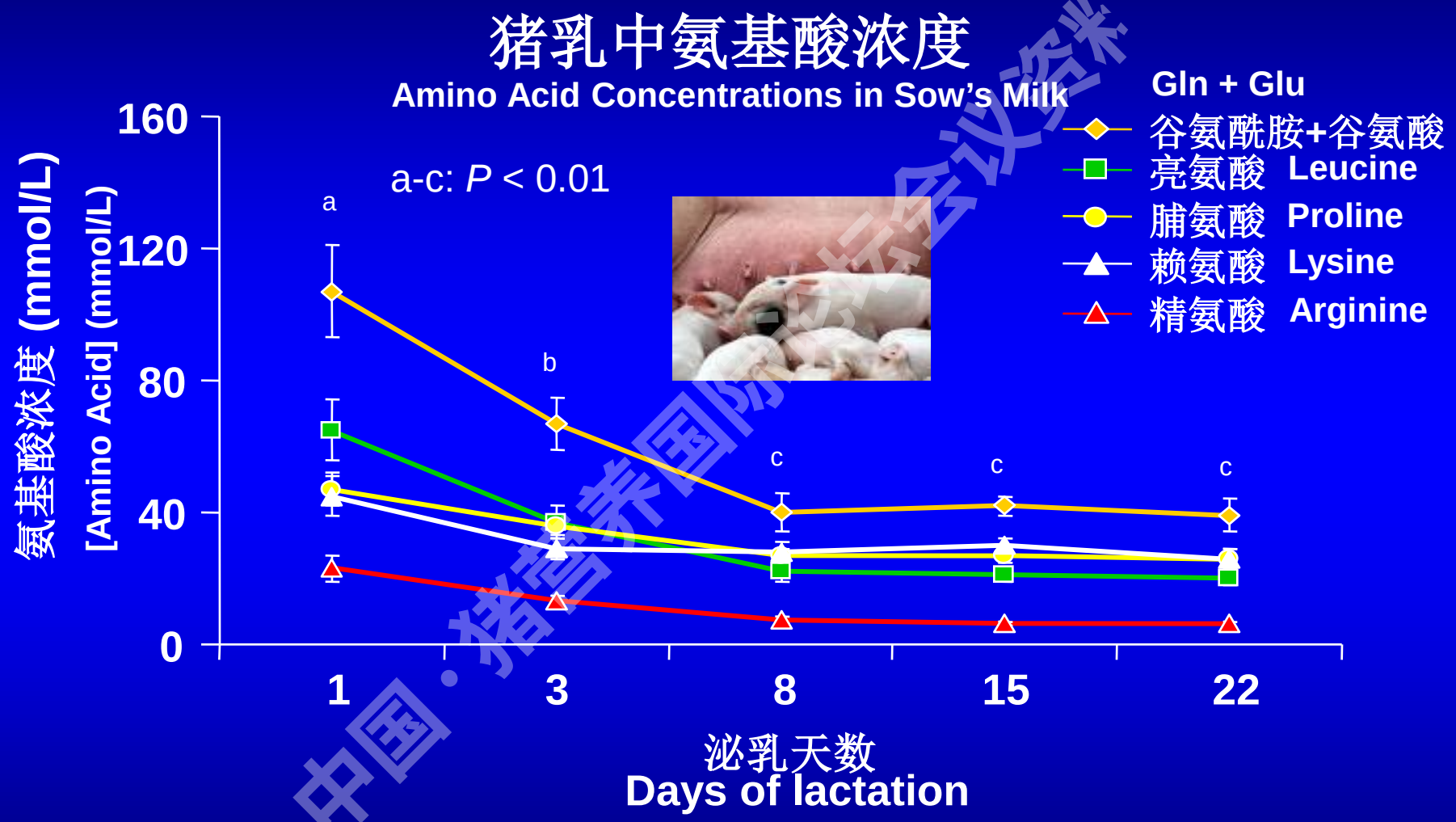
Texas A&M University

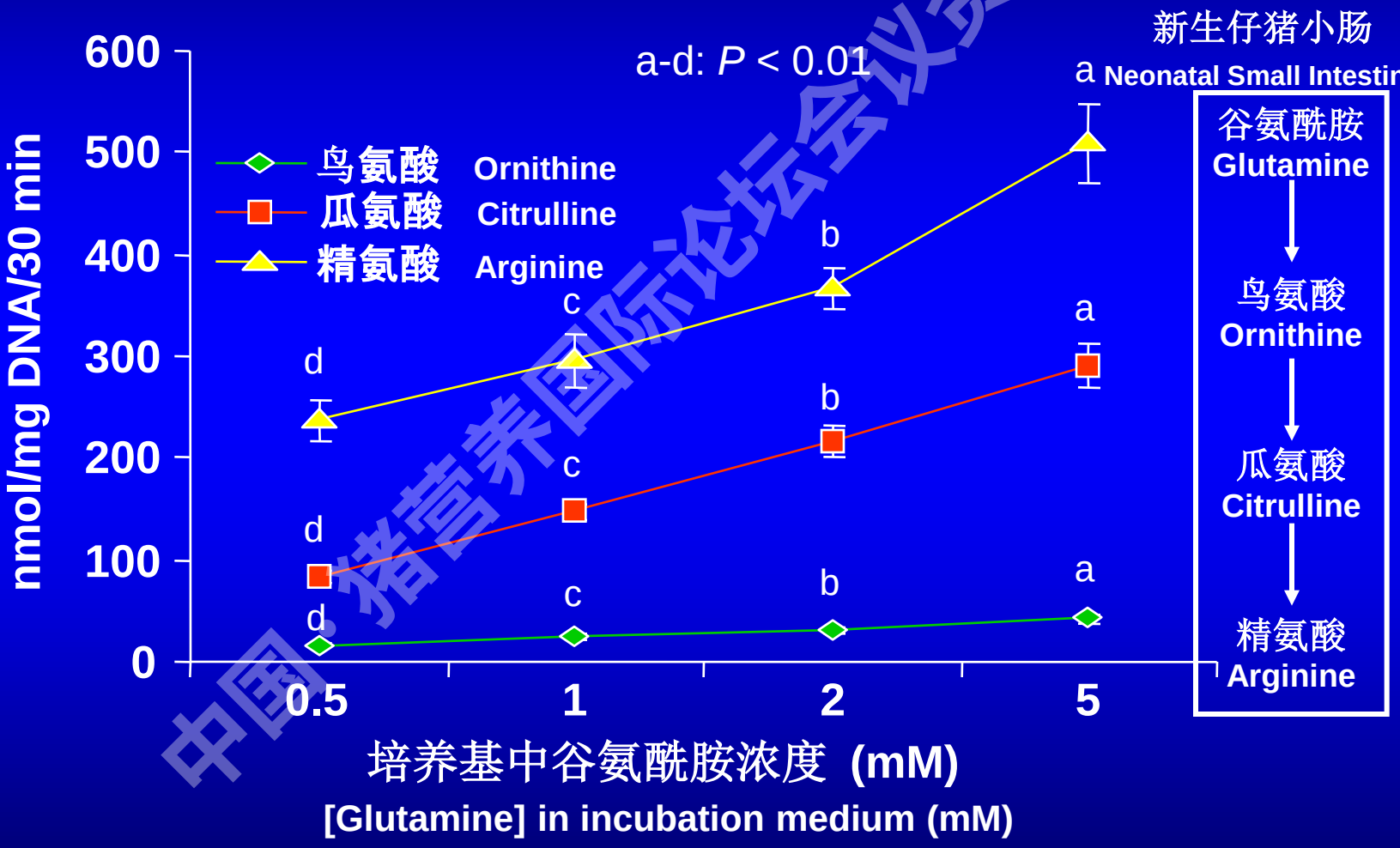
本课题源于1991年的一项非相关研究
The Story Began With an Unrelated Study in 1991



Wu G and Knabe DA (1994) J Nutr 124:415-424

两日龄母乳喂养仔猪小肠细胞中以谷氨酰胺为底物的精氨酸合成

Synthesis of Arginine from Glutamine in Enterocytes of 2-Day-Old Sow-Reared Pigs



Wu G and Knabe DA (1995) Am J Physiol 269:R621-629

Dr. Wenbin Tuo
(Dr. Fuller Bazer的博士后)
Postdoc Fellow of Dr. Fuller Bazer
我的中国农业大学同学
My Classmate at CAU

Dr. Fuller Bazer
(繁殖生物学杰出教授)
(Distinguished Professor of Reproductive Biology)

1993年的一个周六上午，Tuo博士问我一个重要问题：

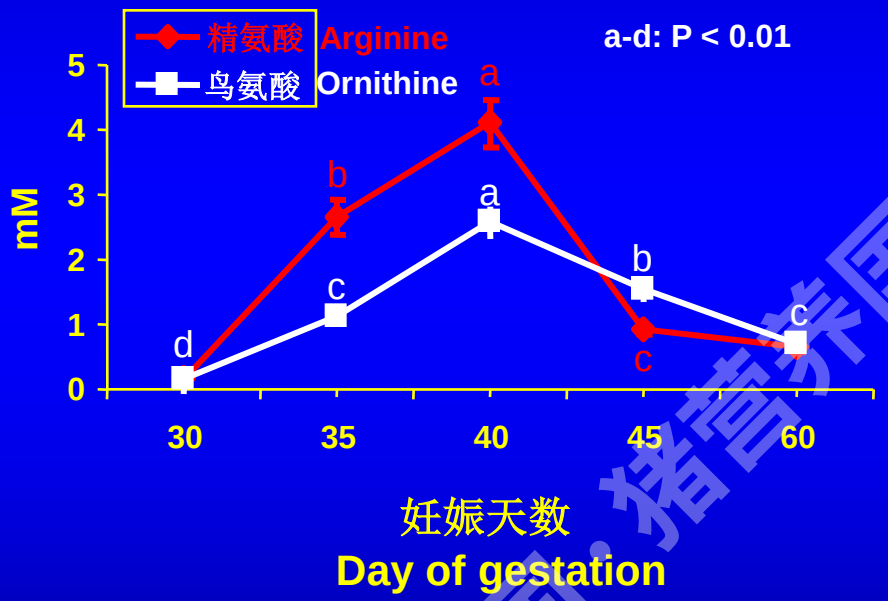
“胎儿究竟能否合成精氨酸？”

On a Saturday morning in 1993, Dr. Tuo asked me an important question: “Can the Fetus Synthesize Arginine?”

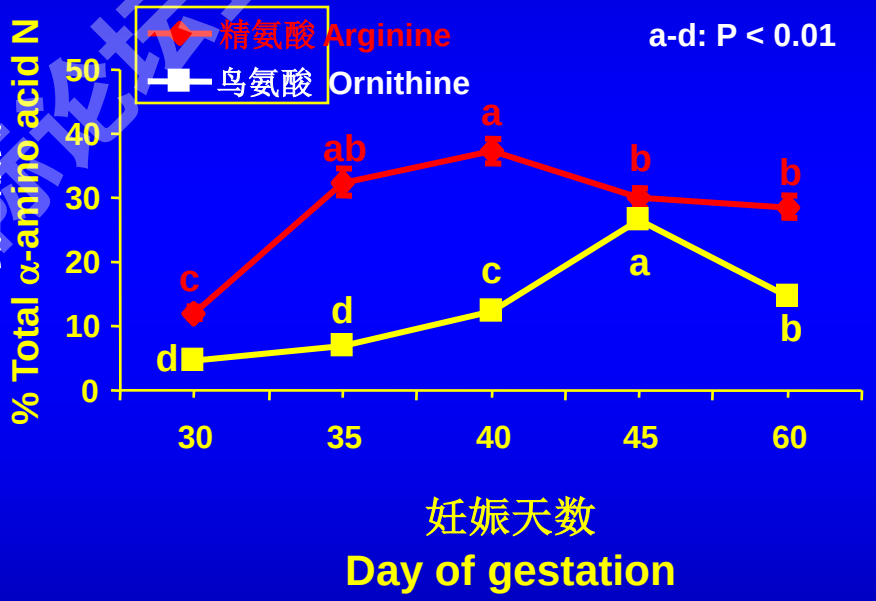
母猪尿囊液中高丰度精氨酸的发现

Discovery of Unusual Abundance of Arginine in Porcine Allantoic Fluid

40天孕龄母猪精氨酸和鸟氨酸浓度 (4 - 6 mM) **Concentrations (4 - 6 mM) of arginine and ornithine on Day 40**



精氨酸和鸟氨酸源氮丰度 (40 – 50%) **Abundance (40 – 50%) of arginine and ornithine nitrogen**



母体血浆中精氨酸浓度 = 0.1 mM
Maternal Plasma [Arginine] = 0.1 mM

Wu, Bazer, Tuo, and Flynn (1996) *Bio Reprod* 54:1261-1265

哺乳动物孕体中精氨酸家族异常高丰度富集的生理学意义是什么？

What is the physiological significance for the unusual abundance of the arginine family in the mammalian conceptus?

BH_4, 四氢生物蝶呤 tetrahydrobiopterin
NO, 一氧化氮 nitric oxide
NOS, 一氧化氮合成酶 nitric oxide synthase
(Ca^{2+}, Calmodulin, FAD, FMN)

Palmer et al. (1988) *Nature* 333: 664-666

一氧化氮的作用 Roles of NO

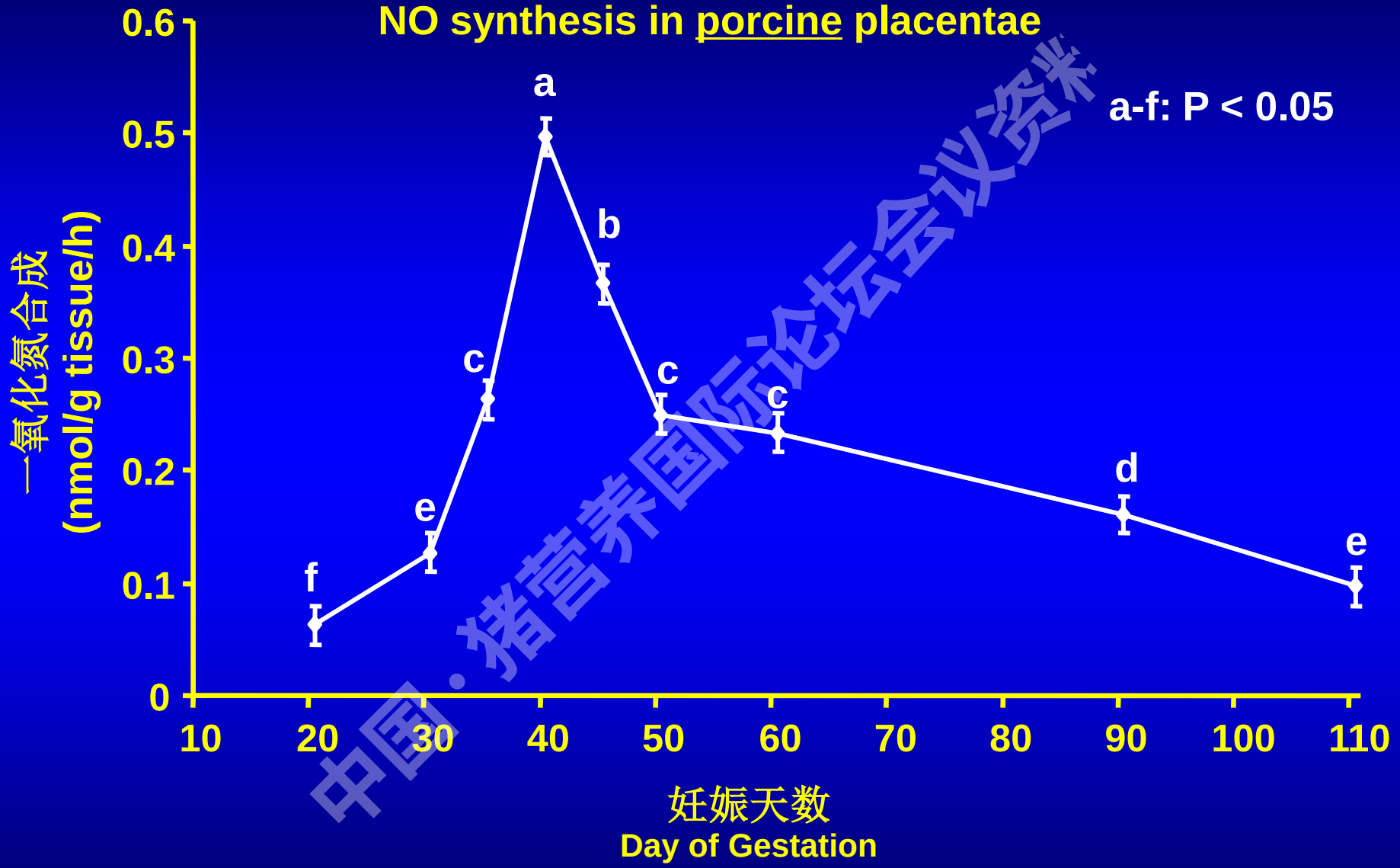
- 血管生成 Angiogenesis
- 胚胎发育 Embryogenesis
- 血管扩张剂 Vasodilator
- 免疫应答媒介 Mediator of the immune response
- 神经递质 Neurotransmitter
- 信号分子 Signaling molecule
- 激素分泌调节子 Regulator of hormone secretion

（例如：胰岛素，生长激素，催乳素，胎盘泌乳素）
(e.g., insulin, GH, prolactin, and placental lactogen)

Flynn, Meininger, Haynes, Shi and Wu (2005) *Diet and Cell Signaling*

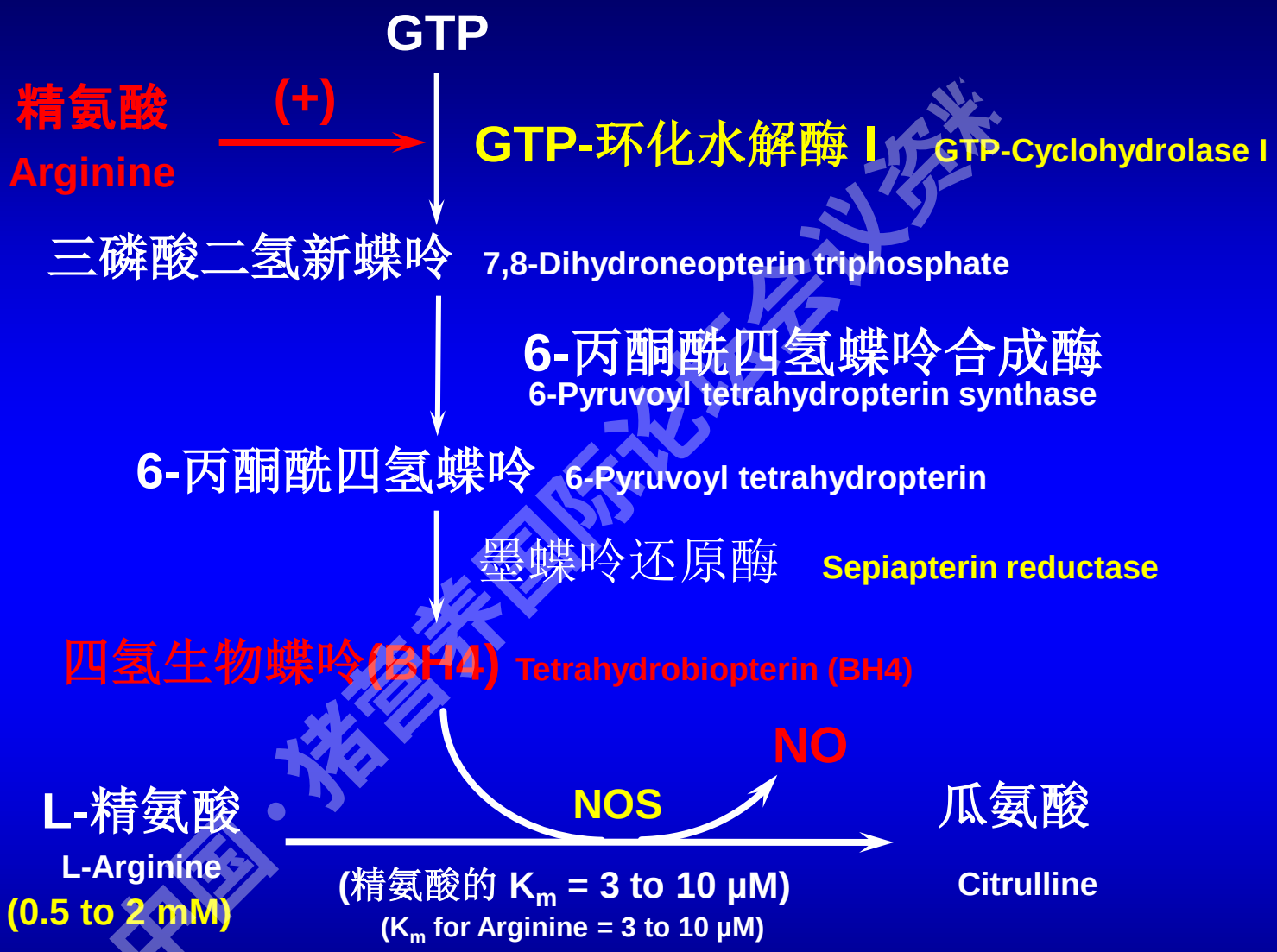
猪胎盘中一氧化氮的合成

NO synthesis in porcine placentae



Wu et al. (2005) *Biol. Reprod.* 72: 842-850.

Wu et al. J Anim Sci 2010



胎盘中精氨酸通过增加可利用四氢生物蝶呤（BH4）含量从而促进一氧化氮合成

Arginine Increases NO Synthesis by Enhancing BH4 Availability in Placenta

在营养学和生理学中，精氨酸还发挥着其他哪些作用？

What Does Other Roles Arginine Play in Nutrition and Physiology?

精氨酸是合成多胺的前体

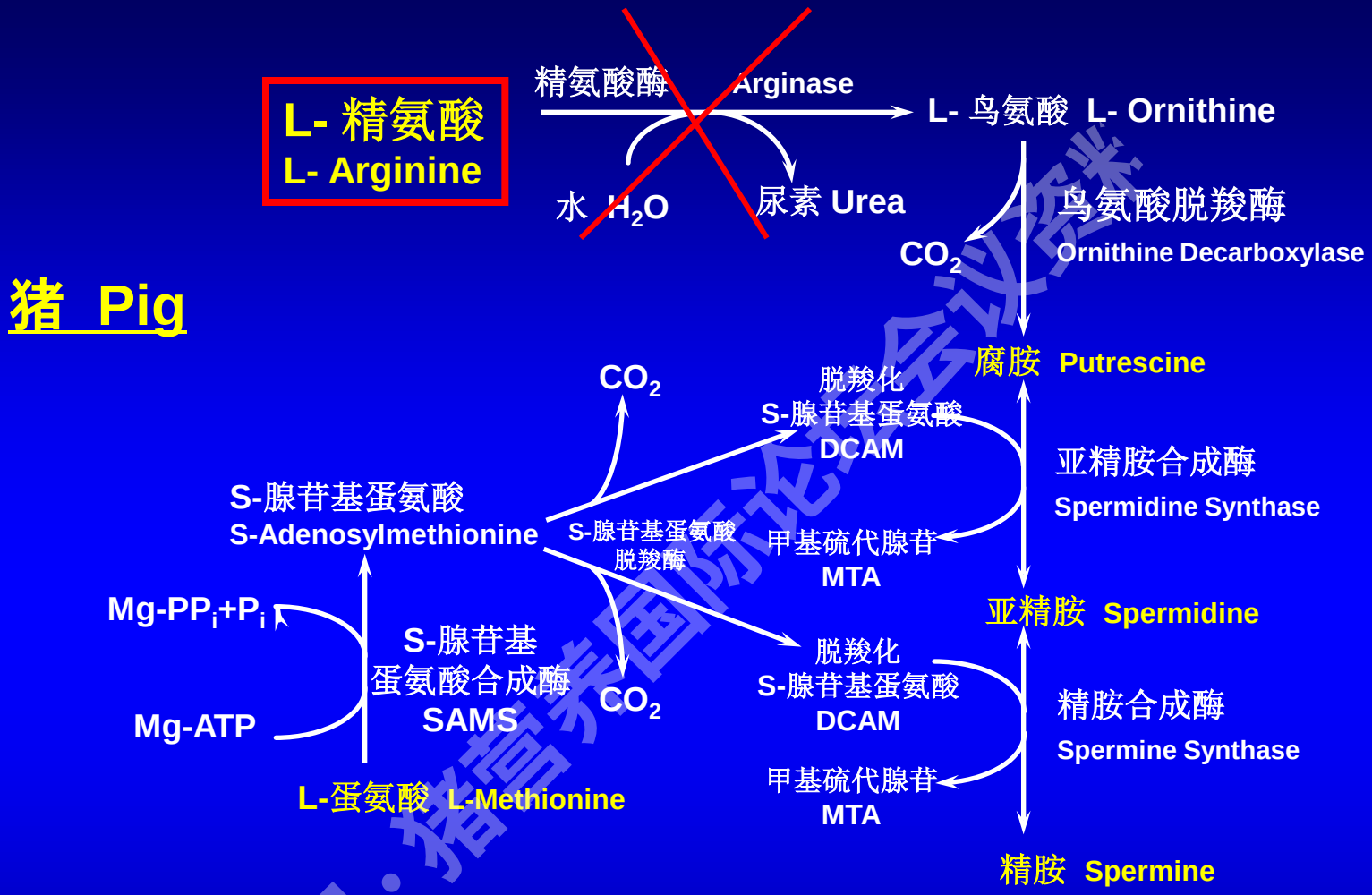
——生物化学课本

Biochemistry Textbooks: Arginine Is the Precursor of Polyamines.

1 = 精氨酸酶 Arginase

2 = 鸟氨酸脱羧酶, 亚精胺合成酶，精胺合成酶

Ornithine Decarboxylase, Spermidine Synthase, and Spermine Synthase



猪胎盘中无精氨酸酶

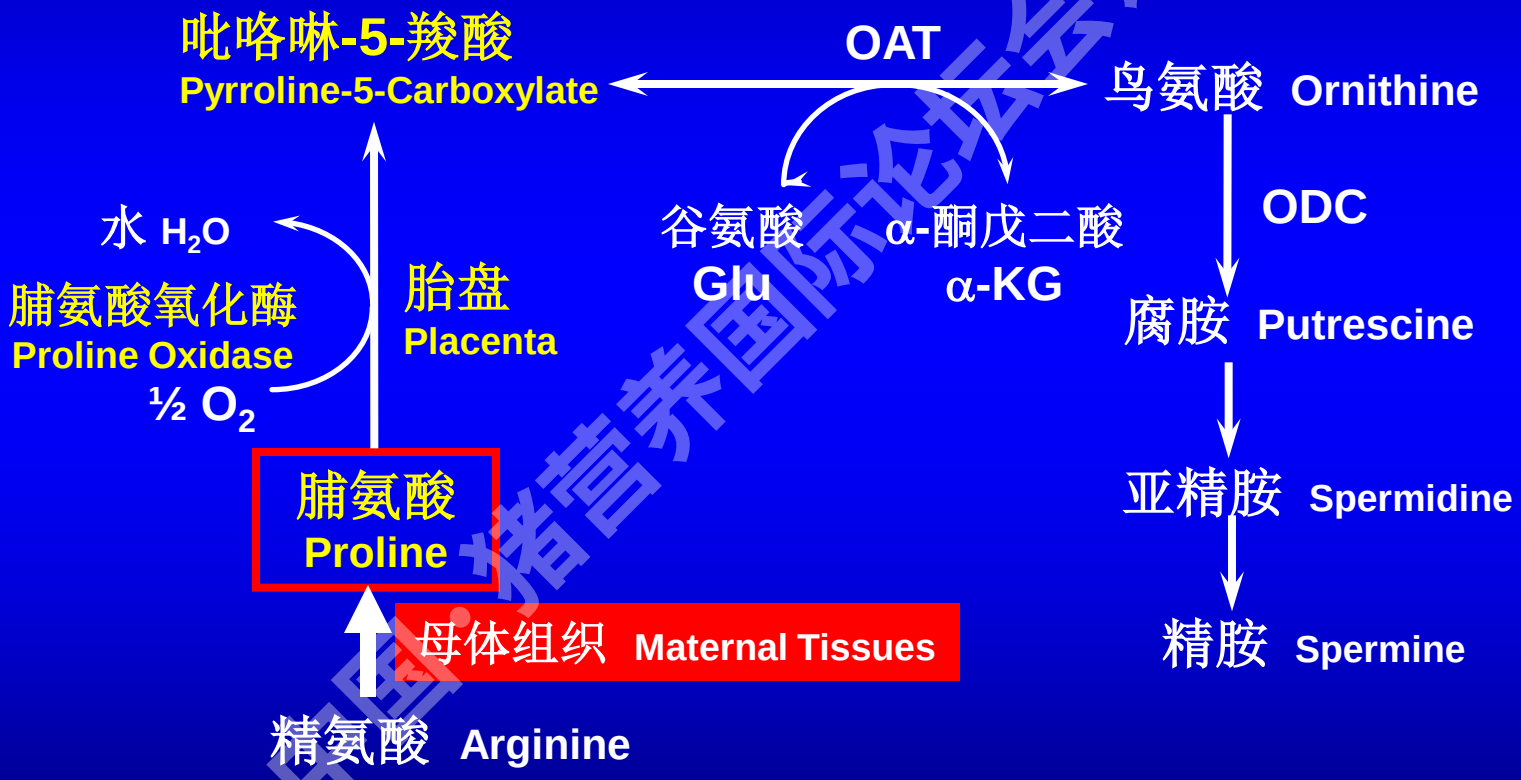
Absence of arginase from the porcine placenta

Wu et al. (2005) Biol Reprod. 72: 842-850

Wu et al. (2005) Biol Reprod 72:842-850

猪胎盘中脯氨酸作为多胺合成底物

Proline as a substrate for polyamine synthesis in the porcine placenta

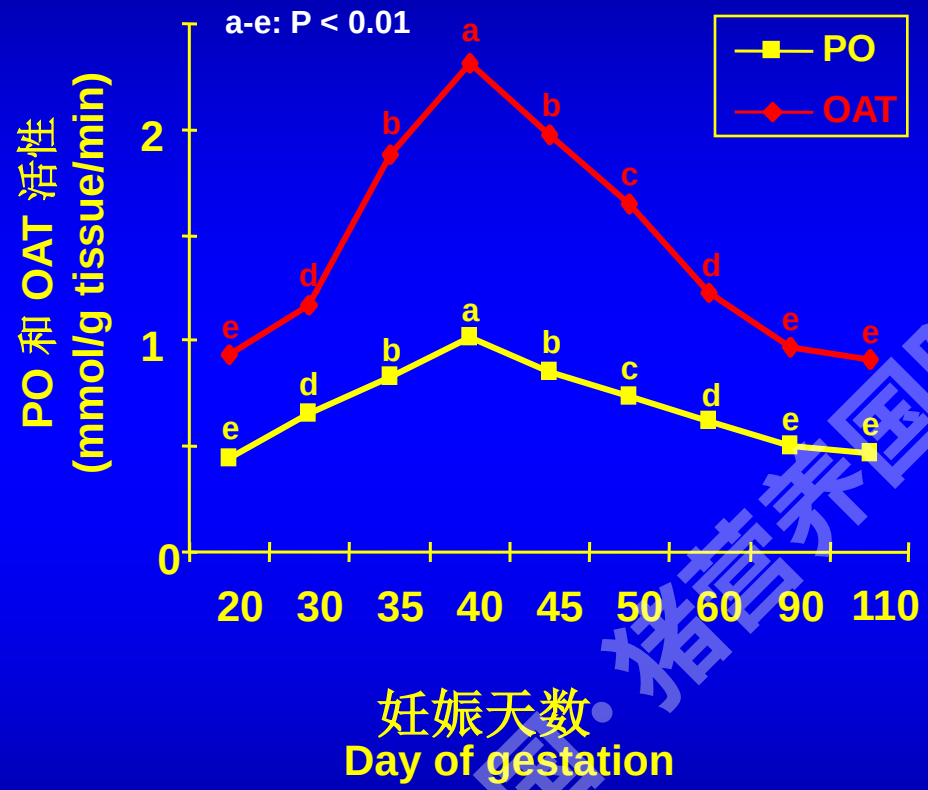


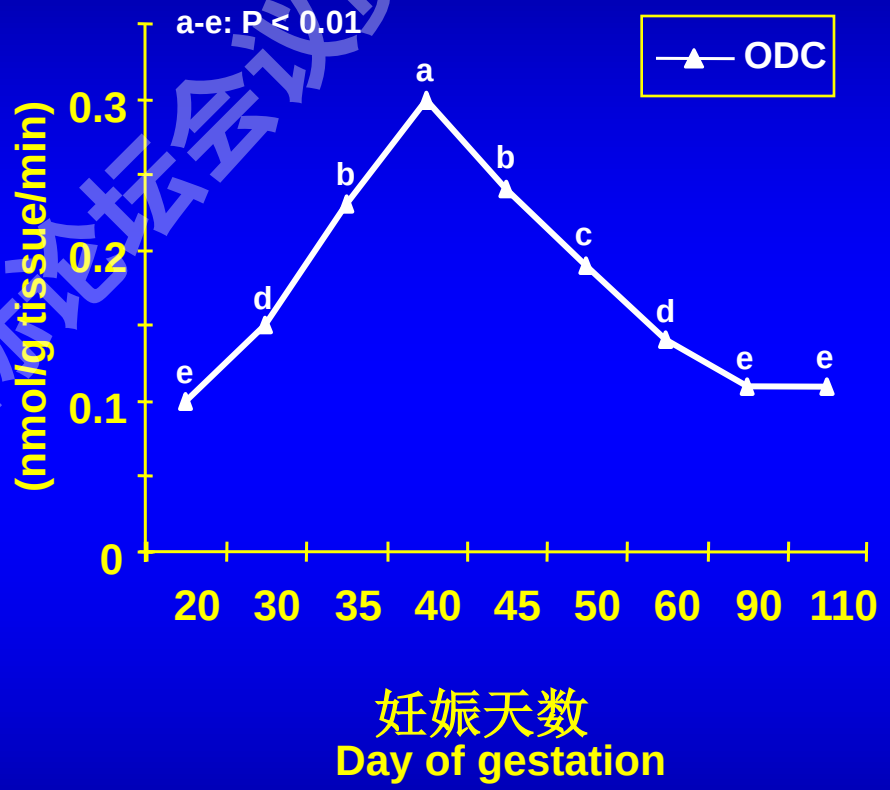
OAT = 鸟氨酸氨基转移酶 ornithine aminotransferase

ODC = 鸟氨酸脱羧酶 ornithine decarboxylase

猪胎盘中脯氨酸氧化酶 (PO)、鸟氨酸氨基转移酶(OAT)及鸟氨酸脱羧酶(ODC)的活性

Proline oxidase (PO), OAT and ODC activities in pig placenta

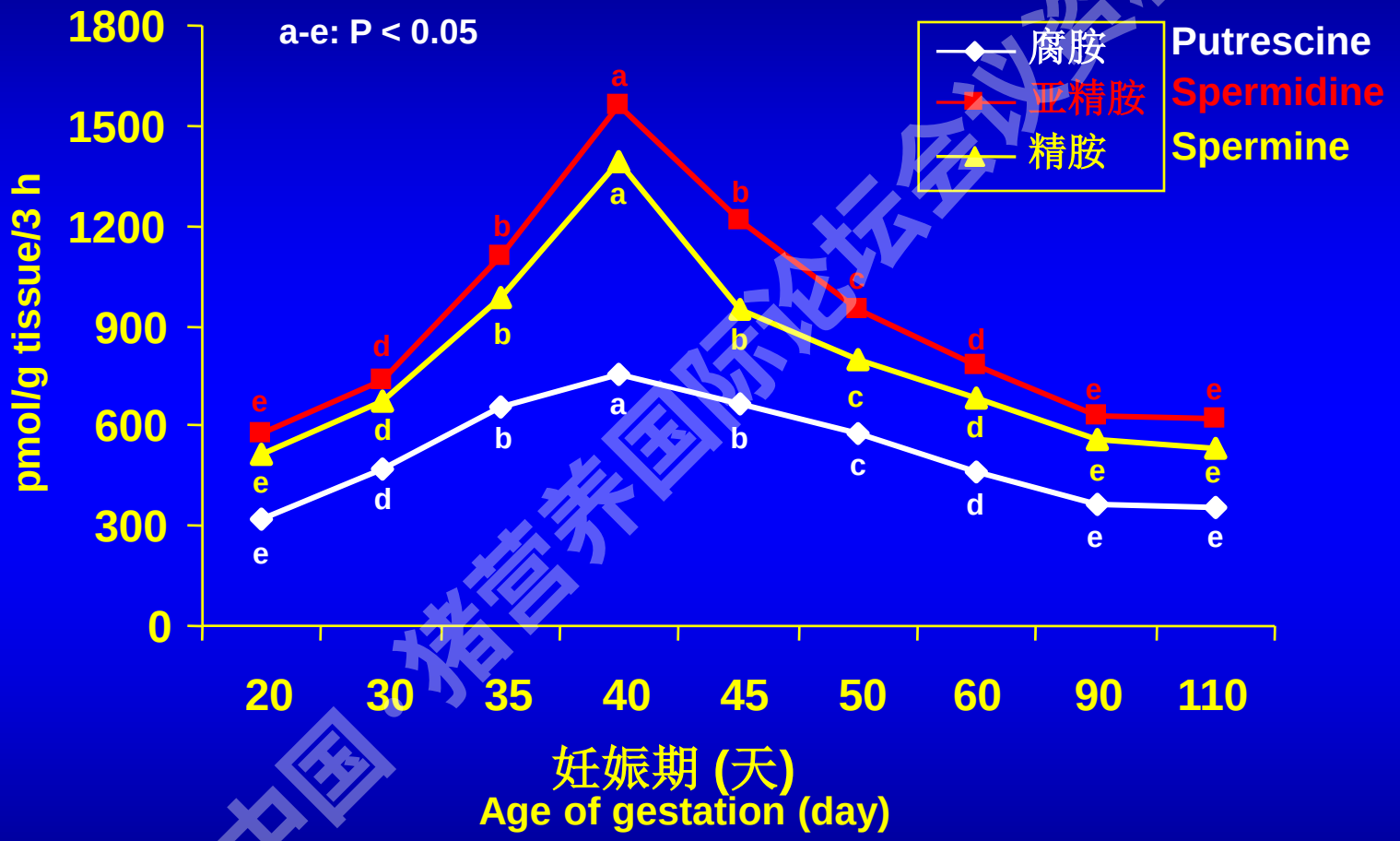




Wu et al. (2005) Biol Reprod 72: 842-850.

猪胎盘中以脯氨酸(2 mM)为底物的多胺合成

Synthesis of polyamines from proline (2 mM) in pig placenta

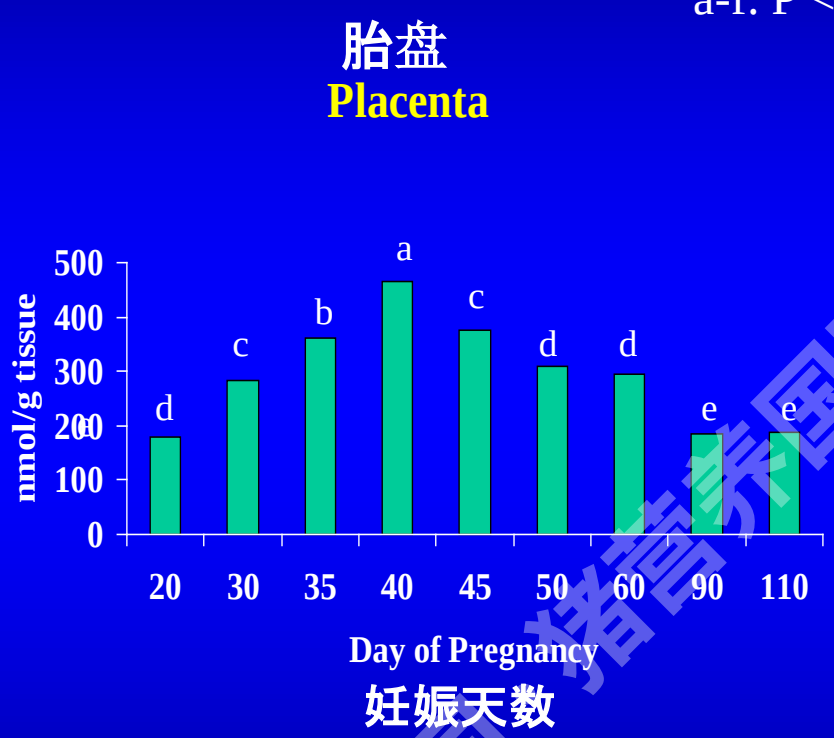


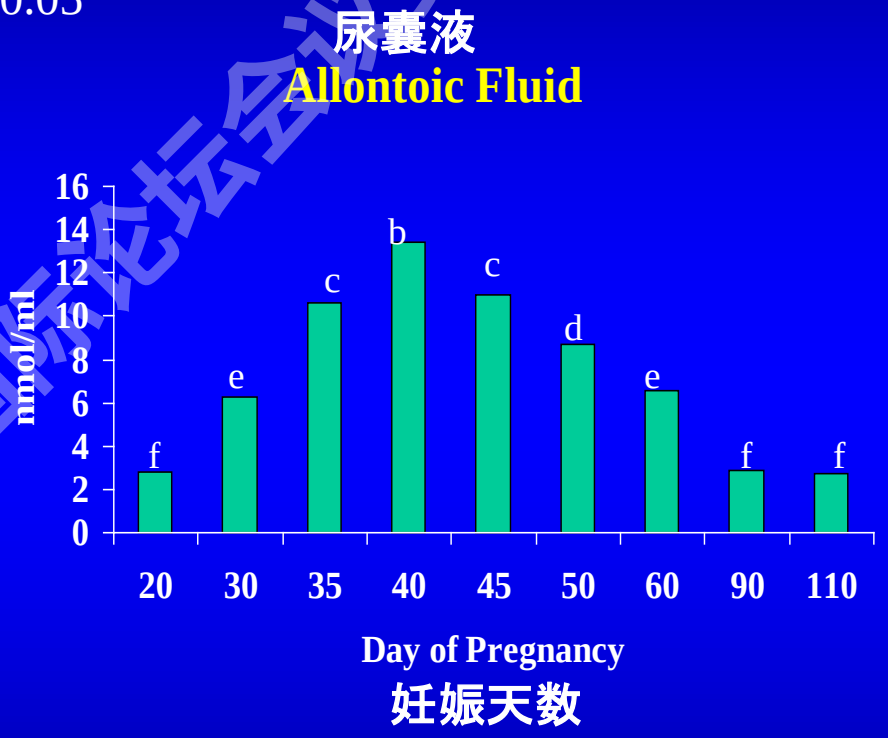
Wu et al. (2005) Biol Reprod 72: 842-850.

猪孕体（胎儿+胎盘）中多胺浓度

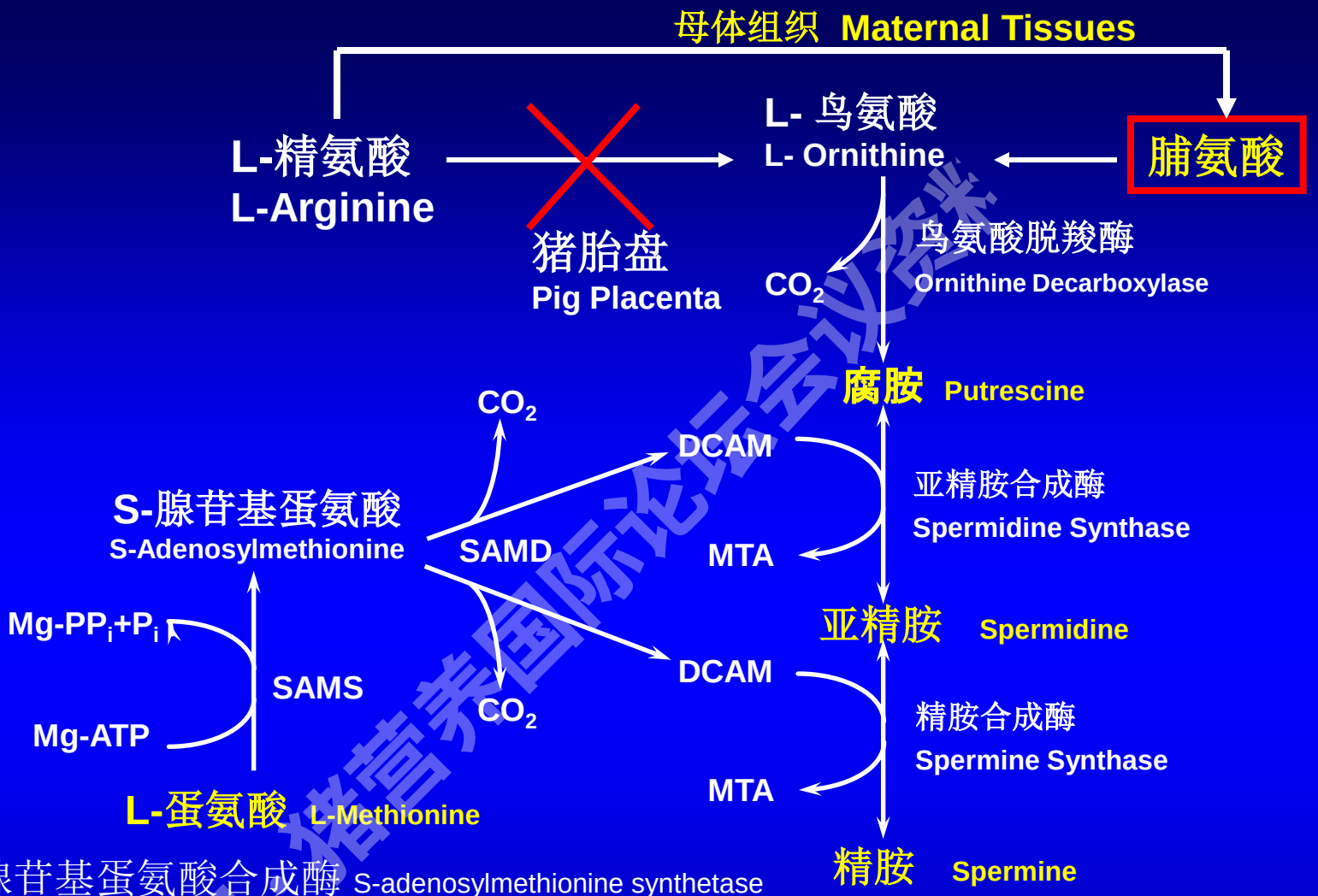
Concentrations of Polyamines in the Porcine Conceptus

a-f: P < 0.05





Wu et al. (2005) Biol Reprod 72: 842-850.



SAMS, S-腺苷基蛋氨酸合成酶 S-adenosylmethionine synthetase
SAMD, S-腺苷基蛋氨酸脱羧酶 S-adenosylmethionine decarboxylase
DCAM, 脱羧化S-腺苷基蛋氨酸 decarboxylated 5-adenosylmethionine
MTA,甲基硫代腺苷 methylthioadenosine

精氨酸对猪体内多胺合成具有重要作用

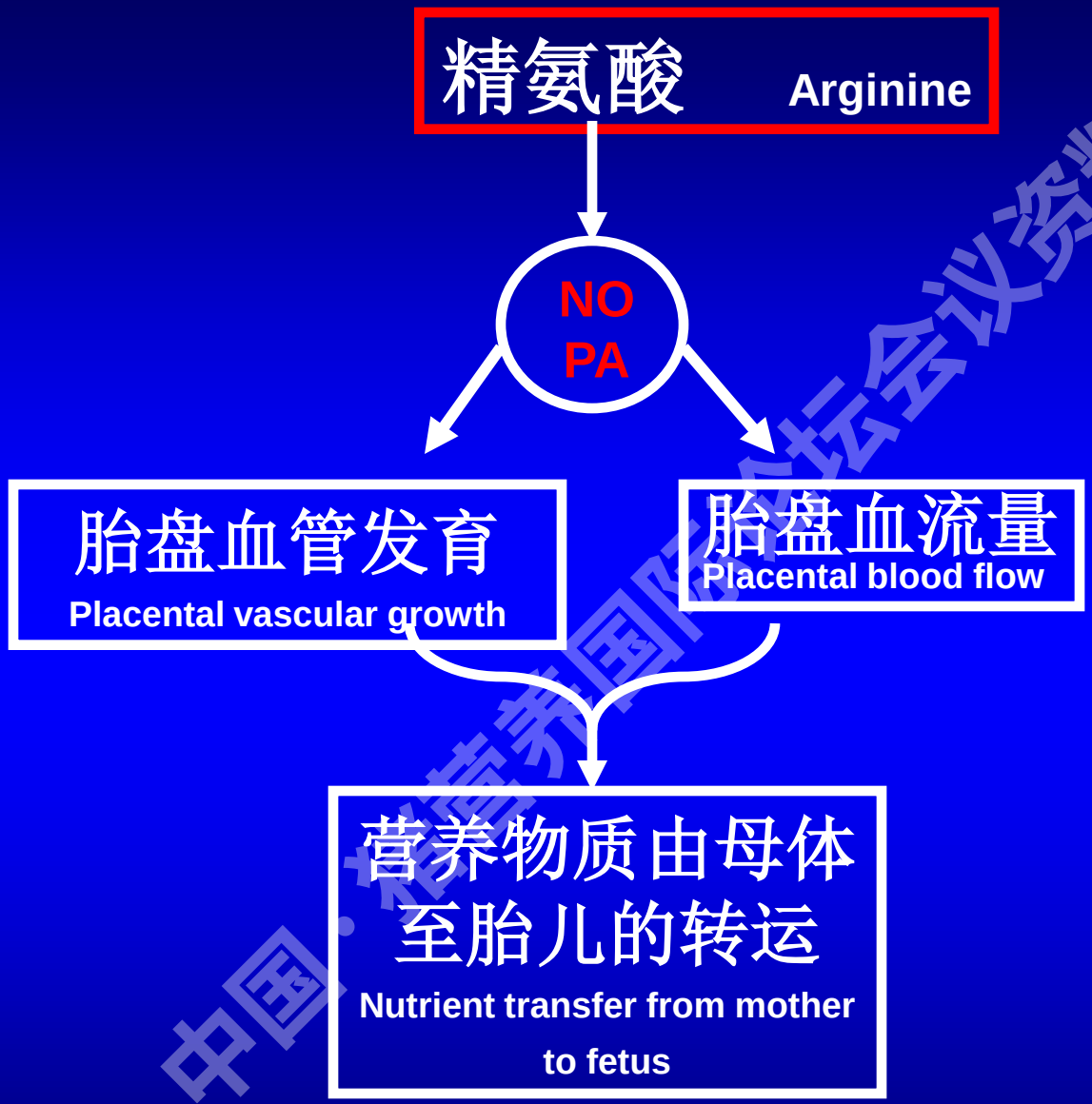
An important role for arginine in polyamine synthesis in pigs

Wu et al. (2000) *Am. J. Physiol.* 279: E395-402

多胺的作用 Roles of polyamines

- 基因表达 Gene expression
- DNA和蛋白质合成 DNA and protein synthesis
- 离子通道作用 Ion channel function
- 细胞凋亡 Apoptosis
- 信号传导 Signal transduction
- 细胞增殖与分化 Cell proliferation and differentiation
- 血管生成 Angiogenesis
- 胚胎发育 Embryogenesis

Wu et al. (2009) Amino Acids 37: 1-17



Wu et al. J Nutr 134: 2169-2172, 2004.

NO = 一氧化氮 Nitric Oxide
PA = 多胺 Polyamines

胎盘血管生成
Placental Angiogenesis

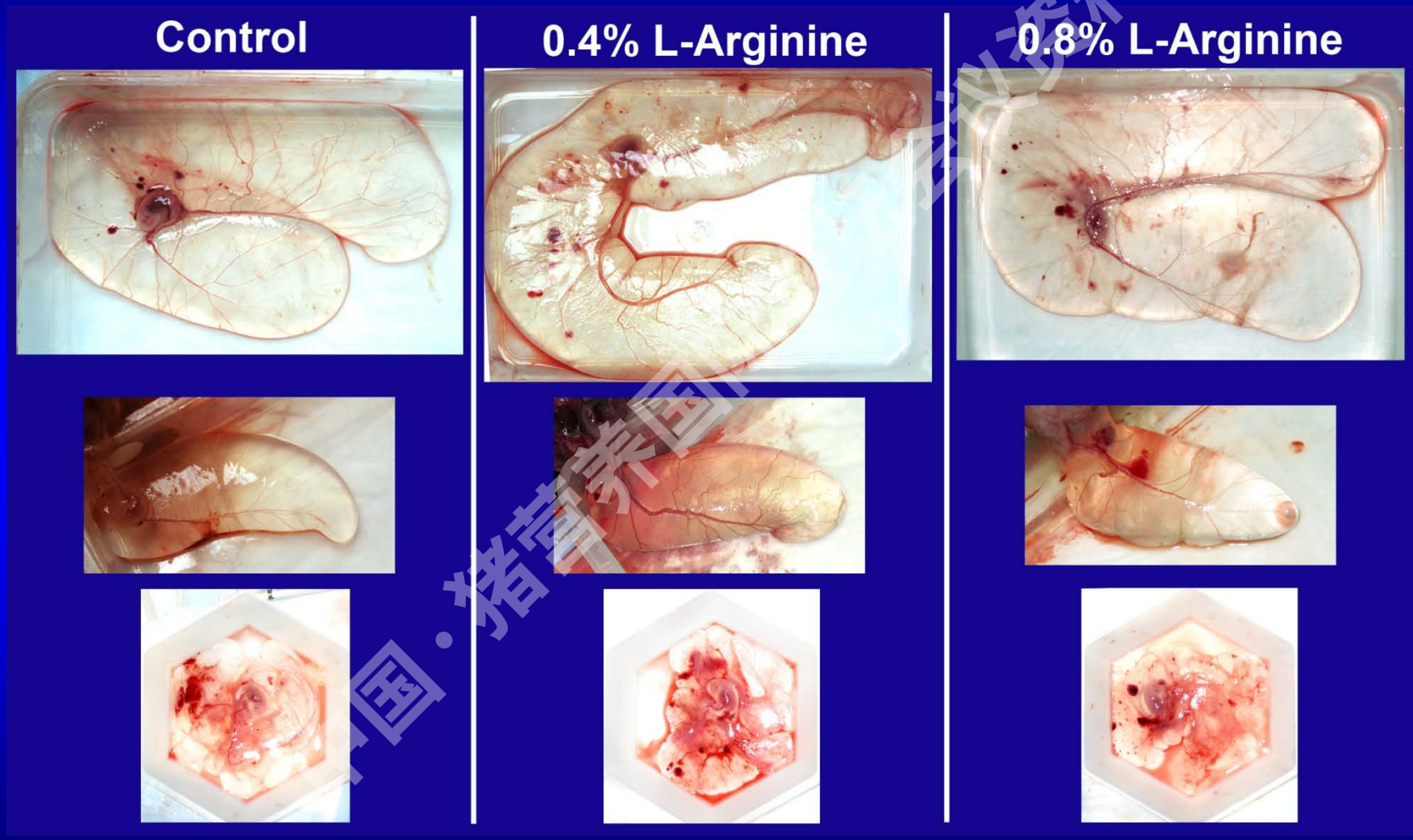
Dr. Fuller Bazer

Dr. Robert Burghardt

Dr. Greg Johnson

精氨酸添加促进猪胎盘血管生成

Arginine supplementation enhances angiogenesis in pig placentae



Li XL, Bazer FW, Johnson GE et al (2010) J Nutr

是否可通过研究精氨酸代谢途径从而提高哺乳动物的繁殖性能？

Can we exploit the arginine pathways to improve pregnancy outcome in mammals?

以猪的宫内发育迟缓（**IUGR**）为研究模型探讨上述问题。

We addresses this question using the porcine model of intrauterine growth retardation (IUGR).

宫内发育迟缓与胎儿的存活率

Intrauterine Growth Retardation (IUGR) and Embryonic/Fetal Survival in the Pig

在哺乳动物中，猪的宫内发育迟缓症最为常见。

The pig exhibits the most severe naturally occurring IUGR among mammalian livestock species.

此外，母猪怀孕期间胎儿死亡率高达50%。

Additionally, the pig suffers from up to 50% of embryonic/ fetal loss during pregnancy.

Wu et al. J Anim Sci 84: 2316-2337, 2006.

仔猪出生体重分布 Distribution of Piglet Birth Weights

窝数 (n) Litter size (n)	116
仔猪总数(n) Total number of piglets born (n)	1,302
出生体重, kg Birth weights, kg	
0.50 – 0.69	3.4%
0.70 – 0.89	8.0%
0.90 – 1.09	13.5%
1.10 – 1.29	30.9%
1.30 – 1.49	27.3%
1.50 – 1.69	14.1%
1.70 – 1.80	2.8%

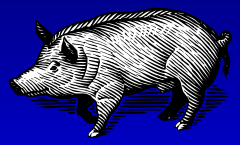
超过75%的仔猪死亡率归咎于IUGR。

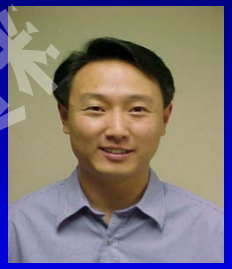
IUGR accounts for > 75% of neonatal deaths.

Wu et al. (2010) J Anim Sci

日粮中添加L-精氨酸促进猪胎儿发育

Dietary L-Arginine Supplementation Enhanced Fetal Growth in Pigs

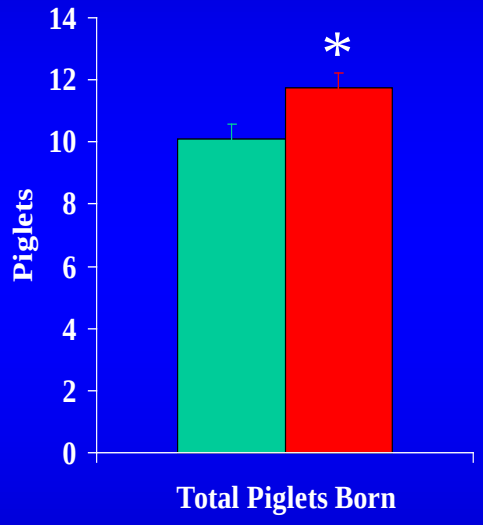


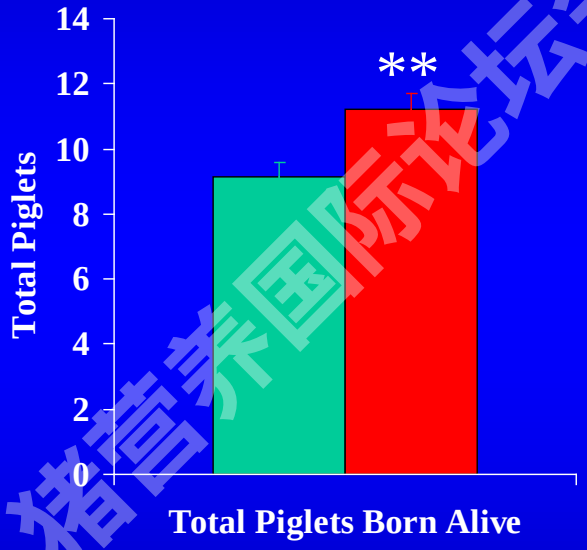


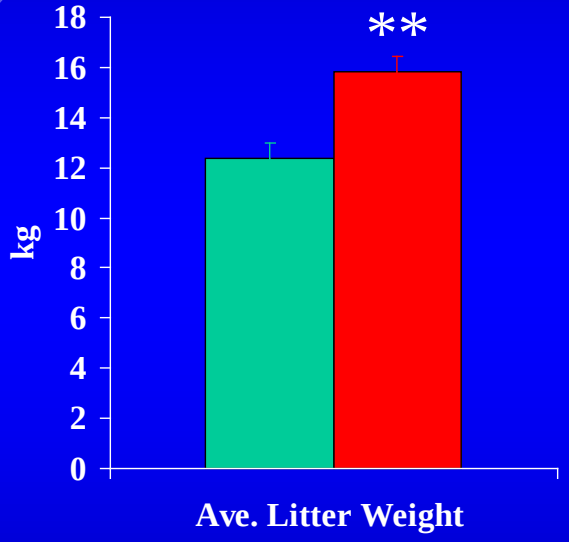
Dr. S.W. Kim
Texas Tech

* P=0.10
** P<0.03

丙氨酸 Alanine　　精氨酸 Arginine







妊娠期30至114天，初产母猪饲喂添加1%L-精氨酸或等氮含量的丙氨酸的玉米-大豆型日粮。**16.6 g 精氨酸/d/头. Arg/Lys = 2.5**

Gilts (n = 53) were fed a corn- and soybean meal-based diet supplemented with 1% L-arginine-HCl or isonitrogenous L-alanine between Days 30 and 114 of gestation.

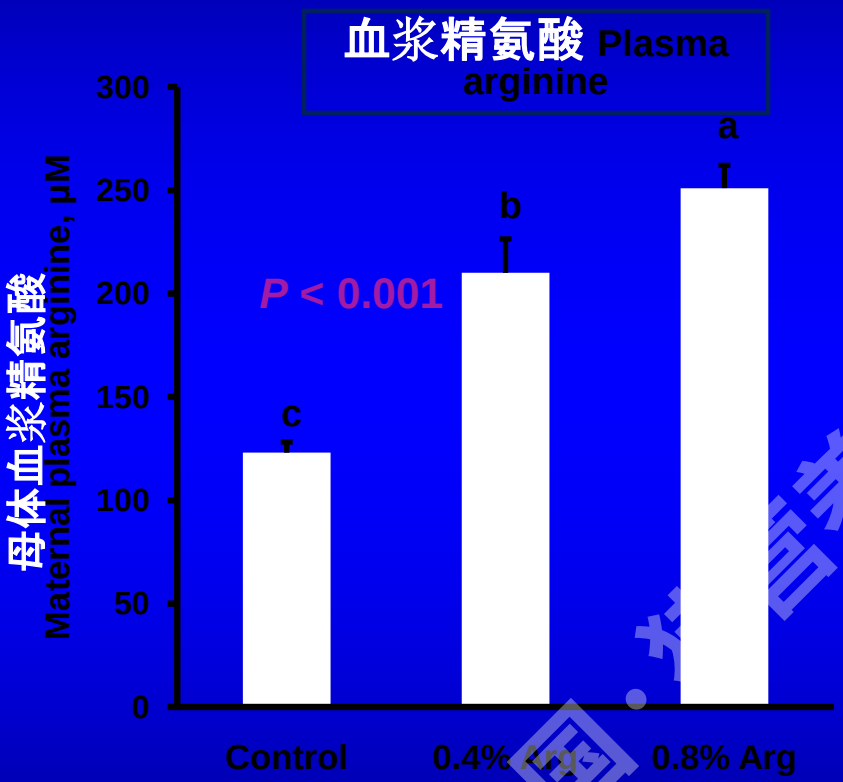
Mateo R, Wu G, Bazer FW et al. (2007) J. Nutr. 137: 652-656.

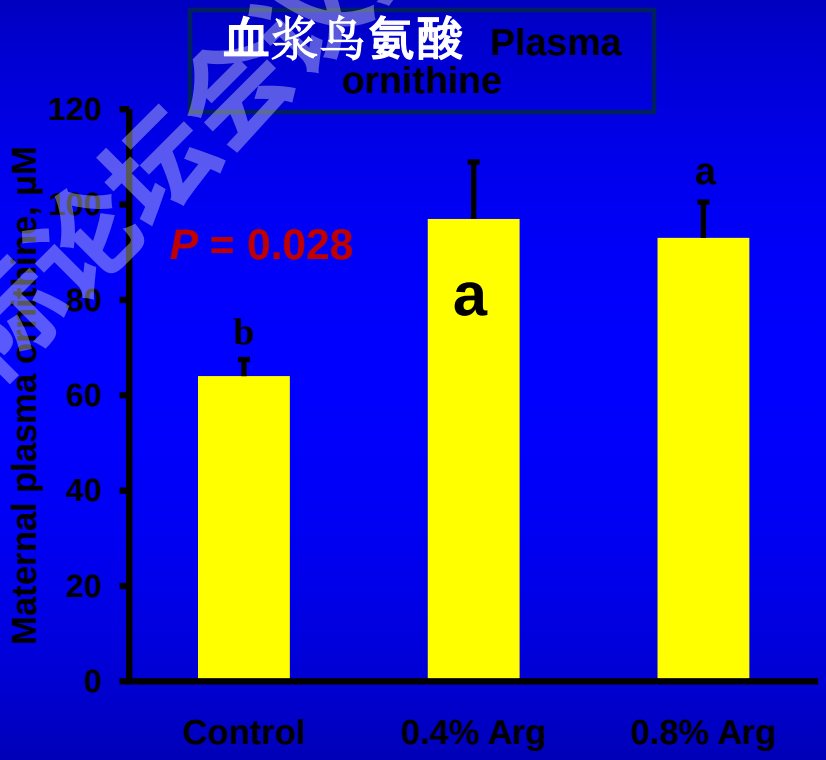
早期怀孕初产母猪的研究 (解剖猪胚胎)

Studies with Early Gestating Gilts (Dissection of the Fetal Pigs)

14-28 d的初产怀孕母猪日粮中添加精氨酸

Dietary Supplementation with Arginine between d 14-28 of Gestation in Gilts





Li X, Bazer FW, Wu G (2011)

14-28 d的初产怀孕母猪日粮中添加精氨酸

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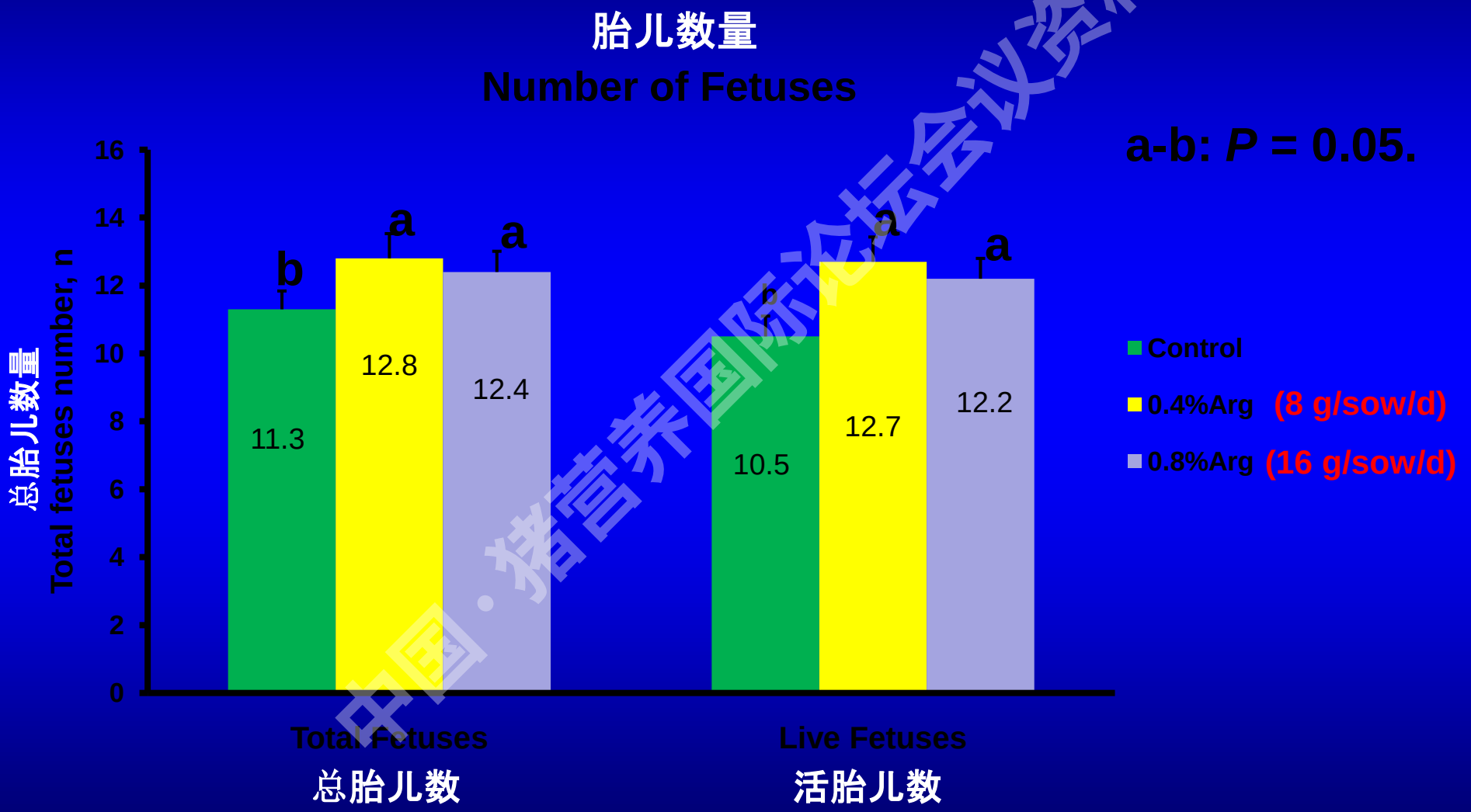


我们的发现与世界各地的科学家证实的结果一致
(14 – 28 d 所有的研究结果，除了Jiang ZY的研究结果)

Our Findings Were Confirmed by Scientists Worldwide

(d 14 – 28 for all studies except for Jiang ZY)

Nutreco, The Netherlands (2006) J Anim Sci 84(Suppl 1):394

Campbell R. New Zealand (2009) www/nzpib.co.nz

De Blasio M. Australia (2009) www.australianpork.com.au

Bee G. Switzerland (2010) Animal 4:1680-1687

Yin YL. Changsha, China (2011) Amino Acids 42:2111-2119

Jiang ZY. Guangzhou, China (2012) Amino Acids 42:2207-2214

(d 25 – 114)

两项研究结果不一致: (既无正效应也无负效应)

Inconsistent with Results of Two Studies: (either no effect or adverse effect)

1. Boyd RD. 2012. J Anim Sci. 90(Suppl 2):34 (Abstract)

2. Allee GL. 2012. J Anim Sci. 90(Suppl 2):33-34 (Abstract)

两项研究的试验设计相同: Same experimental design for both studies:

-- 基础日粮: 0.51% – 0.53% SID Basal diet: 0.51% – 0.53% SID

-- 精氨酸添加量(27.6 g/母猪/d) Supplementation with arginine (27.6 g/sow/day)

无论是怀孕前期 (d 18-34) 还是后期(d 75-115)

during either early (d 18-34) or late (d 75-115) gestation

常见问题: Common Problems:

(1) 日粮中Arg/Lys > 3.5. 造成AA不平衡 & 拮抗.

Arg/Lys in diet > 3.5. Causing AA imbalance & antagonism.

(2) 胚胎着床易损失期 (d 14-18). Missing the period of embryonic implantation (d 14-18).

(3) 日粮蛋白质含量没有数据. No data on protein content in diet.

精氨酸是怀孕母猪的营养性必须氨基酸

Arginine as a Nutritionally Essential Amino Acid for Gestating Sows

例如头胎母猪日粮中添加0. 42% 精氨酸

e.g., 0.42% Arginine in the diet for 1st parity Sows

猪营养需要(第11版)

Nutrient Requirements of Swine (11th Edition)

NRC 2012

添加精氨酸可提高产仔数（2头活仔猪/母猪）

Arginine Supplementation Increases Litter Size (Two Live-born Piglets/Gilt)

生物学和经济学意义： **Biological and Economical Significance:**

活仔猪数的遗传力非常低（0.06-0.09）。1980至2000年间，美国母猪的产仔数每年仅提高0.052头，即：1头仔猪/20年。我们的研究表明通过营养调控可以明显提高母猪产仔数。 The heritability for the number of live-born piglets (i.e., 0.06 to 0.09) Is very low. Thus, litter size in U.S. swine increased only at the rate Of 0.052 pigs/yr between 1980 and 2000 (1 piglet/20 years). Our work has made it possible to greatly enhance litter size through nutritional management.

经济收益：每头仔猪的净收益为$ 45（NPPC 2005）。

Economic returns: Net profits of $45/piglet (NPPC 2005).

这些研究结果已用于指导其它哺乳动物（包括鼠，牛，羊和人类）的研究。

Results of our pig study has guided research with other mammalian species, including rats, cattle, sheep and humans.

USDA/NRI January 15, 2008

Wu et al. (2010) J Anim Sci

母源性营养对胎儿程序化的影响

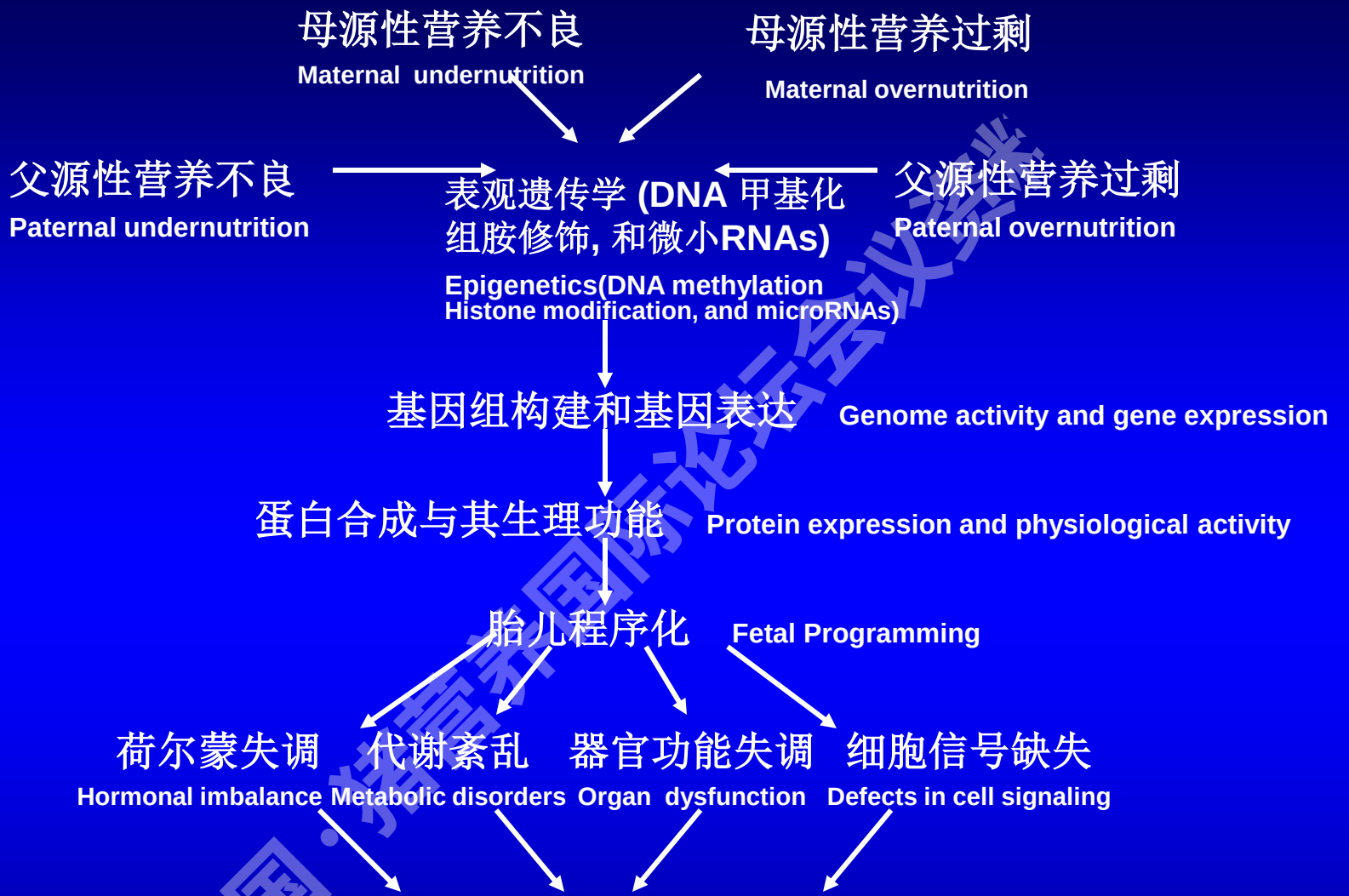
Impacts of Maternal Nutrition on Fetal Programming

胎儿程序化: 在胎儿出生前发育关键时期，营养和其他环境因素能够影响其生长发育途径，从而改变其出生后个体生长代谢以及更为深远地影响其成年后对慢性疾病的易感性。

Fetal Programming: An adaptive process whereby nutrition and other environmental factors alter developmental pathways during the critical period of prenatal growth, thereby inducing changes in postnatal metabolism and susceptibility of adults to chronic disease

影响: 出生后生长发育、营养转换效率、肉品质、繁殖性能，免疫功能和对传染性疾病的易感性

Impacts on: Postnatal growth, development, food efficiency, meat quality, reproduction, immune function, and susceptibility to infectious diseases



Wang et al. (2012) Antioxid Redox Signal

上述研究引发的启示
Lessons from Our Animal Studies

1)一个看似漠不相关的研究，引发出一个重要的发现，即：精氨酸-一氧化氮以及精氨酸-多胺代谢通路在增加哺乳动物产仔数和促进胎儿生长方面发挥着关键作用 An unrelated study led to the seminal discovery that the arginine-NO and arginine-polyamine pathways play an important role increasing litter size and fetal growth in mammals.

2) 术业专攻的团队协作在探索性研究和研究生教育中发挥至关重要的作用 Combination of expertise through team work is very important in discovery research and graduate education.

3) 动物营养学家应运用创造性思维为孕期动物研发出新型日粮
Animal nutritionists should think outside of the box to develop the next generation of improved diets for gestating animals.

致谢 Acknowledgments

Texas A&M University

Dr. Fuller Bazer
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