STUDIES IN THE JUVENILE MINIPIG

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STUDIES IN THE JUVENILE MINIPIG

Advantages of minipigs for juvenile studies
Development of the minipig
Disadvantages
Normal histological appearances in juvenile minipig

I am going to deal with the Gottingen minipig
ADVANTAGES OF MINIPIGS FOR JUVENILE STUDIES

Similarity to human

- Lack fur
  - Cardiovascular system may be less sensitive than dog

Ethical considerations

- In comparison with primates

Supply

- Litter size
  - 5-6
- Litters per year
ADVANTAGES OF MINIPIGS FOR JUVENILE STUDIES

Piglets are very practical for technical procedures, from PND1

- Sows are amenable to human interventions on their offspring
- Administration (oral, IV bolus, dermal)
  - Veins visible the 1st week of age, then less so, due to fattening
  - Central venous catheter can be implanted from PND 3
    - Jugular vein
- ECG recording from PND 5
- Ophthalmoscopy
  - Possible from PND 4
    - Eyes are open at birth so could be possible even earlier
- Blood sampling (microsampling)
DEVELOPMENT OF THE MINIPIG

Critical period for organogenesis: gestation days 11 – 35

Epitheliochorial placenta
  • Proteins cannot cross from mother

Born with eyes open, able to walk, haired, some teeth erupted

Cannot thermoregulate at birth
  • little subcutaneous fat
  • pigs lack brown fat

Passive uptake of colostral Ig A, G & M on PND 1 only

Require Fe supplementation to maintain blood hemoglobin level
  • poor Fe storage in piglet liver
  • Little Fe in sow’s milk
  • Lab piglets have no access to Fe from rooting in soil

Weaned at PND28

Rapid post-natal growth

Puberty at approximately 6 months old

Epiphyseal growth plates close after 18 months old
DISADVANTAGES OF MINIPIGS FOR JUVENILE STUDIES

Liable to several (rare) spontaneous pathological syndromes

**Thrombocytopenia**

in farm pigs, is a disease of piglets
colostral antibodies target platelet antigens from sire
in minipigs, from 7 weeks old, but can occur in adult

**Glomerulonephritis**

can be seen at 4 months old (Vezzali et al 2011)

**Cholecystitis**

Are well developed at birth

Much critical organ development has already taken place
NORMAL HISTOLOGICAL APPEARANCES IN JUVENILE MINIPIGS

| Liver        |
| Spleen      |
| Small intestine |
| Kidney      |
| Brain       |
| Reproductive system |
LIVER, SPLEEN, ILEUM

Adult appearance, even at PND 15
LIVER

PND 15
LIVER

PND 15
PND 34 Pigment is not present in all animals at this age
ILEUM

PND15
<table>
<thead>
<tr>
<th>Minipig</th>
<th>PND 1</th>
<th>Basophilic nephrogenic zone with immature tubules lined by blastemal cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PND 15</td>
<td>kidney appears mature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No immature nephrons</td>
</tr>
<tr>
<td>Human</td>
<td>PND 1</td>
<td>Nephrogenic zone has disappeared</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• there are many subcapsular glomeruli</td>
</tr>
<tr>
<td></td>
<td>In infancy</td>
<td>growth of subcapsular tubules forms a subcapsular layer free of glomeruli</td>
</tr>
<tr>
<td>Rat</td>
<td>Kidney not mature until PND 30</td>
<td></td>
</tr>
</tbody>
</table>
KIDNEY

Gestation Day 60
Gestation Day 110. Note cuboidal podocytes & blastemal tubule cells
Paraventricular primary germinal matrix is similar at PND15 to that in adult
FOREBRAIN

PND 15

PND 63
FOREBRAIN
Subtitle (Calibri, size 18)

PND 15

PND 148 (adult in tox study)
Cerebellar external granular layer
  • Humans: disappears at 6 to 12 months old
  • Rat: remnants still present at PND 21
  • Minipig:
    • still present at PND 63
    • absent by PND 148
CEREBELLUM

PND 15
CEREBELLUM

External granular layer

PND 15
CEREBELLUM

External granular layer

PND 63
CEREBELLUM

PND148
(adult in tox study)
Further study needed of post-natal myelination in minipigs

In humans, myelination not complete until at least 2 years old

In rats, myelination of brain continues into adulthood
  • Downes & Mullins (2014) Tox Path 42, 913-922

In pigs, myelination can be decreased by influences in utero
  • Swine fever virus
    • Middle third of pregnancy
  • Trichlorfon
TESTES

Up to birth
   • Only Sertoli cells & spermatogonia

By PND 15
   • A few spermatocytes develop
   • Epididymis: no sperm. Epithelium of head cuboidal

By PND 35
   • More spermatocytes present
   • Epididymis: no sperm. Epithelium of head columnar

By PND 63
   • Most tubules mature
   • Epididymis: sperm present. Epithelium of head tall columnar, ciliated

The present findings agree with those of Taberner et al (Theriogenology 2015)
   • The testes & epididymides of male Gottingen minipigs are histologically mature by 2 months old
TESTES

Gestation Day 60

Note development of Leydig cells

Gestation Day 110
TESTIS & EPIDIDYMIS

PND 15
TESTIS

PND 35
TESTIS & EPIDIDYMIS

PND 63
TESTIS

PND 63

35 | EVERY STEP OF THE WAY
TESTIS

PND 148: adult in tox study
PROSTATE

PND35
- Epithelium immature

PND63
- Epithelium more mature
  - Taller cells
  - Secretion present
PROSTATE

PND 35

PND 63
OVARY

PND 15 and 63

- follicles mostly primordial
  - 1, flattened layer of granulosa cells
  - no zona pellucida

PND 196

- follicles mostly primordial
- some secondary follicles
  - multiple layers of granulosa cells
  - zona pellucida present
- in some animals, vesicular follicles present
OVARY

PND 15
OVARY

PND 63
OVARY

PND 196
### Other Post-Natal Developmental Changes in Humans


<table>
<thead>
<tr>
<th>Organ</th>
<th>Developmental Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Alveologenesis continues from birth to 2 years old</td>
</tr>
<tr>
<td>Gut</td>
<td>GALT and ganglion cells of enteric neural system mature</td>
</tr>
<tr>
<td>Liver</td>
<td>Some bile ducts (distant from hepatic hilus) are embryonic at birth, but all mature by 1 month old</td>
</tr>
<tr>
<td></td>
<td>Bile ducts and hepatic arterial system become fully mature at 15 years old</td>
</tr>
</tbody>
</table>
OTHER POST-NATAL DEVELOPMENTAL CHANGES IN HUMANS

Pancreas
- some embryonic inter- and intra-lobular connective tissue remains at birth, but has disappeared by adulthood
- endocrine cells are more abundant in the neonate, and not all grouped within islets

Adrenal cortex
- the 3 zones of the definitive cortex become distinct from each other in the first months after birth
  - inner cortex (secretes DHEA) well-developed in fetus
  - involutes over 1st 2 months after birth
  - present in humans & some NHPs

Thyroid
- the gland is more active at birth than in the adult
  - smaller follicles with less colloid; follicular cells cuboidal

Pituitary
- calcified concretions present in anterior lobe until 6 months old
OTHER POST-NATAL DEVELOPMENTAL CHANGES IN HUMANS

Subtitle (Calibri, size 18)

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**Thymus**

involutes after puberty

**Spleen**

Germinal centres, mantle & marginal zones do not form until after birth (due to antigen exposure). Similar in lymph nodes

**Skeletal muscle**

Fibres at birth are more rounded than in the adult
Minipigs are practical non-rodents for juvenile studies
   amenable to handling & dosing
   males become sexually mature early
Post-natal development of several organs is similar to humans
Minipigs are even more mature at birth than are humans
   so some human developmental stages might be missed in a juvenile
   minipig study
Post-natal development of various organs should be compared with the human to
find the best species and comparable ages
THANKS

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