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Review article

# Which precocial rodent species is more suitable as the experimental model of microgravity influence on prenatal musculoskeletal development on international space station?

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A R T I C L E I N F O

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A B S T R A C T

The International Space Station (ISS) has the possibility to perform experiments regarding rodent reproduction in microgravity. The musculoskeletal system at birth in precocial rodent species more resembles the human than that of altricial rodent species. For precocial rodent species with body weight ≤ 500 g (limit of ISS) determined were: adult body mass, newborn body mass, head-body length, tail length, existing variants (wild, domesticated, laboratory), single/group housing, dry food consumption/24 h, water intake/24 h, basal metabolic rate mlO2/g/h, environmental temperature, sand baths, urine output ml/24 h, fecal output g/24 h, size of fecal droplet, hair length, life span, length of oestrus cycle, duration of pregnancy, building nest, litter size, stage of musculoskeletal maturity at birth, and the duration of weaning. Characteristics were obtained by searching SCOPUS as well as the World Wide Web with key words for each of the species in English, Latin and, local language name. These characteristics were compared in order to find most appropriate species. Twelve precocial rodent species were identified. There is not enough data for Common yellow-toothed cavy, and Eastern spiny mouse. Inappropriate species were: Gundis, Dassie rat are a more demanding species for appropriate tending, litter size is small; Octodon degus requires sand baths as well as a nest during the first two weeks after delivery; muscle maturity of Spiny mouse at birth (myotubular stage), does not correspond to the human (late histochemical stage); Chinchilla requires separately housing, daily sand baths, has upper limit of weight. Possibility of keeping Southern mountain cavy as pet animal, short estrus, large litter size, absence of the need for nest and sand baths, makes this species the most promising candidates for experiments on ISS. If an experiment is planned with exposing gravid animals before term of the birth, then they might be kept together in the existing Rodent Habitat (USA). If an experiment with birth in microgravity is planned on ISS, the existing habitats do not provide conditions for such an experiment. It is necessary to develop habitats for separate keeping of pregnant animals to enable the following: 1. undisturbed delivery 2. prevent the possibility of hurting the newborns 3. ensure adequate post-partum maternal care and nursing.

## Introduction

Although humans lack the technical capabilities to reproduce during space flight and colonize the solar system at this point in time, it is likely that in the future human species will be able to overcome these limitations. Besides ionizing radiation, the major problem in human

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reproduction is the altered gravitational regime. In preparation for these future perspectives, it is necessary to learn about the effect of microgravity, hypogravity and hypergravity on intrauterine development of the mammalian experimental animals before human pregnant females will be exposed to altered gravitational conditions. Most prominent changes in astronauts are related to deconditioning of the musculoskeletal system, muscle hypotrothy and osteopenia (Tanaka et al., 2017).

The first experiments in microgravity with pregnant mammals were with altricial rodents: rats and mice. Pregnant rats were exposed to microgravity in missions: Cosmos 1514 (13–18 gestation day (GD)) (Serova, 2001), NIH Rodent 1 (9–20 GD) (Ronca, 2003), and NIH Rodent 2 (11–20 GD) (Ronca, 2003). Pregnant mice have been flown only once thus far, on the Neurolab mission in 1998 but without detailed post-flight data on these dams or their offspring (Ronca, 2003). After NIH R1 mission, no major alterations in gross morphology of rats thigh muscles development have been observed (Clark et al., 1995). Data after Cosmos 1514 shows shorter ossified areas, between 13% and 20%, in all bones (Denisova, 1986), although different source stated that ossified areas were shorter only for 3–4%, and was not adequately investigated (Serova, 2001). On the other side, data from NIH R1 mission shows no significant effect on developing foetal skeleton ossification (Serova et al., 1996).

To go one step further in experimental research it is necessary to present data related to physical characteristics of the intrauterine development as well as the consequence of decreased muscle loading on bones during development. The physical environment is not the same during the whole period of gestation in rats. A significant increase of fetus/amniotic fluid ratio (weight in mg/volume in μl) is present from the 18th day of gestation onward. In this period, the buoyant force has less effect on the rat fetuses. On the 10th day of gestation this ratio was 0.24, on 11th 0.19, on 12th 0.33, on 14th 0.25, on 16th 1,12, on 18th 2,51 and on 20th 7.12 (Park and Shepard, 1994). Up to the 21–22nd week of gestation, the human fetus is in conditions similar to neutral floating, while after the 26th gestation week, because of the only partial buoyant force, intrauterine apparent weight of the fetus is reduced to 60% –80% of the extrauterine weight (Sekulic et al., 2005).

Rat fetuses paralyzed by daily transuterine injections of curare from day 18 of gestation until day 21 develop fetal akinesia deformation sequence. This syndrome is characterized by: multiple joint contractures, absent movements leads to passive immobilization; pulmonary hypoplasia, intrauterine breathing movements are necessary for lung development; micrognathia and high arched palate, sucking and swallowing movements produce mechanical stress and negative pressure which are required for mandible development and lowering hard palate; fetal growth retardation with bone hypoplasia and osteopenia, mechanical stress generated by movements is necessary for bone growth; short umbilical cords, caused by absent tension forces on the umbilical cord because of absent movements of the fetus; and polyhydramnios, because of absent swallowing of the fetus. Changes in bone affected the shape and transverse growth of the femoral diaphysis as well as metaphysis. There was a decrease in total cross-section area and the reduction of the absolute and relative amounts of bone trabeculae with marked thinning of the periosteum (Rodríguez et al., 1992). Human fetuses are also prone to fetal akinesia sequence in case of muscle weakness or lack of intrauterine space (Shea et al., 2015). Bones of the rat fetus accretes 95% of the required 12.5 mg of calcium in the last five days of gestation (Kovacs, 2006). The total amount of calcium increases from the original 5 g to 30 g in human fetuses during the last trimester of gestation (Kovacs, 2006).

Also, chronic polyhydramnios, an excess of amniotic fluid volume during the last trimester of gestation, because of buoyancy, reduce the apparent weight of the fetus from physiological 60–80% down to 10–20% of its actual weight (Sekulic et al., 2005). Decreased mechanical stress on musculo-skeletal system because of increased fetal buoyancy could cause bone maldevelopment in human fetuses, as well as non-traumatic fractures (Sekulic and Petkovic, 2019; Nadeau et al., 2019). A parallel to the excess fluid volume during the last trimester of gestation could be dry and wet immersions used as a model of microgravity. In case of dry immersion, a test subject wearing a shirt and trunks was placed on a waterproof fabric and immersed into a liquid analogous to human body tissues by density up to the neck level, in a supine position. The folds of the waterproof fabric allowed the person's body to be enveloped from all sides freely. Wet immersion means that the subject is in direct contact with the liquid bath. Dry and wet immersions cause physical inactivity as well as support withdrawal (Tomilovskaya et al., 2019).

The discrepancy between findings in fetal akinesia deformation sequence from one side and absent structural-anatomical abnormalities of the locomotor system among fetuses exposed to microgravity, on the other side, could be explained with different timing of exposure to decreased mechanical stress. In fetuses exposed to microgravity until the 18th day of gestation, such as in the case of Kosmos 1514, the influence of microgravity is overlapping with a significant effect of buoyancy at 1 g, while the period of intensive bone accretion of the calcium hasn't begun. Missions lasted until the 20th day of gestation, NIH Rodent 1and 2, exposed fetuses for half of the time of dramatic increase of bone calcium accretion.

Exposing rat fetuses to the complete critical period of bone development poses a risk because of birth during spaceflight. Newborns of altricial rodent species are entirely dependent on mothers' care. They are blind and have limited capability of movements. Birth of altricial species in microgravity could be associated with mothers failing to maintain pups within a coherent nest, and nurse newborns. These changes are likely to diminish pup milk intake, warmth, and tactile stimulation, usually provided by the mother (Ronca, 2003). These factors could prevent the survival of altricial rodent species in microgravity.

Conversely, precocial rodent species are fully mature at birth with open eyes, have the ability to find the nipple and feed himself. They are capable enough to support their weight and locomote significant distances. While the rat is born in the myotubular stage of muscle development, human and precocial rodent species guinea pig (*Cavia porcellus*) are born in late histochemical maturation stadium. They possess both types of extrafusal muscle fibers at birth (Sekulic et al., 2006). The sarcoplasmic reticulum of the muscles in *Cavia porcellus* and humans have prenatal maturation, providing appropriate activation profiles for both slow and fast-twitch muscle. In rats at birth the sarcoplasmic system is immature and slow muscles have activation profiles more characteristic of fast muscles (Sekulic et al., 2006). In human and, guinea pig, EMGs shows the phasic and tonic pattern at birth. In the rat, only phasic activity is present at birth, while tonic activity occurs between the 11th and 16th days of life (Sekulic et al., 2006). Considering bone maturity at birth, guinea pigs are also more similar to human newborns than altricial species. Around the 50th day of gestation, of an ∼ 66-day gestation, the long bones of guinea pigs show both primary and secondary ossification centers. At birth, all human long bones have primary ossification centers, whereas secondary ossification centers are present in the distal part of the femur and occasionally in the humerus (Zoetis et al., 2003). In altrical rodent species at birth, only primary ossification centers are present (Zoetis et al., 2003). Osteocalcin levels in human and guinea pig fetuses near birth are significantly higher in comparison with adults. In rats, the increase of this protein occurs only after 20th postnatal day (Rummens et al., 2000). Previously it was suggested that the influence of altered gravitational conditions on the development of the locomotor system significantly varies according to the stage of maturity (Sekulic et al., 2006).Mother-young bonding is bi-directional, linkages are based on maternal care-taking patterns. This early protective behavior with touch, hearing, smelling, and visual stimulation is necessary for establishing neural, behavioral, and physiological organization of the newborn (Ronca, 2003). Since the state of sense maturity in precocial mammals resembles more to that of human, exposing precocial rodents

**Table 1**
Precocial rodent species with adults body mass more than 500 g.

| Species | Common name | Body mass (kg) | Species | Common name | Body mass (kg) |
|---|---|---|---|---|---|
| *Atherurus africanus* | African brush-tailed porcupine | 1.0–4.0 (Nowak, 1999) | *Thryonomys swinderianus* | Greater cane rat | 3–9 (Kingdon et al., 2013) |
| *Atherurus macrourus* | Asiatic Brush Tailed Porcupine | 1.0–4.3 (Nowak, 1999) | *Thryonomys gregorianus* | Lesser cane rat | 2.65–7.5 (Kingdon et al., 2013) |
| *Chaetomys subspinosus* | Bristle-spined rat | 1.3 (Nowak, 1999) | *Hystrix africaeaustralis* | Cape porcupine | 18–30 (Kingdon et al., 2013) |
| *Coendou prehensilis* | Brazilian porcupine | 2.0–5.0 (Nowak, 1999) | *Lagostomus maximus* | Plains viscacha | 2–8 (Kingdon et al., 2013) |
| *Erethizon dorsatum* | North American porcupine | 5.0–14.0 (Nowak, 1999) | *Myocastor coypus* | Nutria | 5–10 (Kingdon et al., 2013) |
| *Castor Canadensis* | North American beaver | 13.0–32.0 (Nowak, 1999) | *Dasyprocta punctata* | Central American agouti | 1–4 (Kingdon et al., 2013) |
| *Castor fiber* | Eurasian beaver | 13.0–35.0 (Nowak, 1999) | *Myoprocta pratti* | Green acouchi | 0.8–1.2 (Kingdon et al., 2013) |
| *Cavia aperea* | Brazilian guinea pig | 0.52–0.795 (Nowak, 1999) | *Anomalurus beecrofti* | Beecroft's flying squirrel | 0.6–0.7 (Kingdon et al., 2013) |
| *Cavia porcellus* | Guinea pig | 0.7–1.1 (Nowak, 1999) | *Anomalurus derbianus* | Lord Derby's scaly-tailed squirrel | 0.6 (Kingdon et al., 2013) |
| *Dolichotis patagonum* | Patagonian mara | 8.12 (Nowak, 1999) | *Pedetes capensts* | South African springhare | 2.8–3.3 (Kingdon et al., 2013) |
| *Kerodon rupestris* | Rock cavy | 0.9–1.0 (Nowak, 1999) | *Pedetes surdaster* | East African springhare | 2.8 (Kingdon et al., 2013) |
| *Hydrochoerus hydrochaeris* | Capybara | 35.0–66.0 (Kingdon et al., 2013) | *Cuniculus taczanowskii* | Mountain paca | 7.0–12.0 (Nowak, 1999) |
| *Sphiggurus mexicanus* | Mexican hairy dwarf porcupine | 1.5–2.5 (Nowak, 1999) | *Cuniculus hernandezi* | Hernández Paca | 6.4 (Nowak, 1999) |
| *Chinchilla chinchilla* | Short-tailed chinchilla | 0.8 (Nowak, 1999) | *Cuniculus paca* | Lowland paca | 7.0–12.0 (Nowak, 1999) |

$X^{n}$ – number of reference.

to microgravity would be a better model to investigate influence of this environment on mother-young human bonding. While the initial approach to investigate the influence of micro- and hypergravity effects on prenatal development was with well-known laboratory animals, altricial rodent species, the next step could include precocial rodent species in order to more close resemble human musculoskeletal development. Rodents and primates belong to the same mammalian clade *Euarchontoglires*, sharing a similar genome. As it was presented, according to maturity of musculoskeletal system at birth, precocial rodent species, *Cavia porcellus*, is more similar to humans than altricial rodent species. Additionally, their newborns may possess the capability to survive the early neonatal period in microgravity. Influence of altered gravitational conditions, including microgravity on prenatal development, was not investigated so far in any precocial rodents. The International Space Station (ISS) represents a unique laboratory because of the possibility of experiments that can include a complete cycle of mammal reproduction in microgravity.

The aim of this paper is to identify which precocial rodent species is more appropriate as an experimental model to investigate influence of microgravity on prenatal musculoskeletal development using existing habitats for rodents on the ISS.

## Material and methods

### *Habitats and laboratory equipment on ISS*

ISS has three rodent habitats. Rodent Habitat (USA) can accommodate 10 mice or up to 6 rats weighing 250 g, with habitable surface area of 5690.3 $cm^2$ (Scofield et al., 2018). The Mice Drawer System (Italy) could house up to 6 mice, and has three configurations of the floor area: 116 mm x 98 mm for three individually housed mice, two cages 178 mm x 98 mm large enough to house two pairs of mice, a separate cage 364 mm x 98 mm for a group of up to six mice (Cancedda et al., 2012). Habitat Cage Unit (JAXA, Japan) can house 6 mice in a microgravity environment and 6 mice in the artificial gravity conditions; each mouse is in a separate module with a floor area of 101 $cm^2$ and 560$cm^3$ in volume. It has a section with a glove box, used for the transfer of mice and waste collection (Shimbo et al., 2016).

The NASA Transporter Unit is used for transfer from the ground laboratory facilities to the Rodent Habitat on the ISS. It has a habitable surface area of 4612.9 $cm^2$ and it can provide for 10 mice or 6 rats (Scofield et al., 2018).

Animal Access Unit is used to transfer animals from the Transporter to the Rodent Habitat and, as warranted, from there to the Microgravity Science Glovebox on the ISS. Its dimensions are the same as NASA Transporters Unit's and it has a glove box for the manipulation with the experimental animals (Scofield et al., 2018).

Other necessary laboratory facilities at ISS allow complex experiments with altricial rodents without special adaptation. Minus Eighty Degree Laboratory Freezer (MELFI) provides capability to stow cell culture 1–10 ml, fluid samples 1–500 ml, specimens/dissection tissues 2–10 ml, specimens (whole) – frozen carcasses 10–500 ml (Cheganças et al., 2007). Total stowage volume is 300 liters, in four independently controlled dewars.

### *Selection criteria of the precocial species*

In the first step, precocial rodent species were identified. Precocial rodents are species which at birth can support their weight; they are mobile from the moment of birth and have open eyes. To identify precocial rodent species, each rodent family was examined individually based on the data provided in two sources (Nowak, 1999; Kingdon et al., 2013). Maximum weight of the *Rattus norvegicus* of 500 g, which is used as an experimental animal on ISS (Otto et al., 2015), as well as maximum 500 ml storage volume for the specimens (whole) – carcasses frozen in MELFI, limits the weight of precocial rodents to 500 g. In the second step, the identified precocial rodents were selected in groups with body mass >500 g and ≤500 g.

In the next step, comparison of the altricial rodent species, rat and mouse characteristics was performed, with the precocial rodent species with ≤500 g body mass, for the purpose of identifying the precocial rodent species which would be the best candidate for future experiments in the microgravity conditions.

The comparison was performed with regards to the physical characteristics of the species (head–body length, tail length, body mass) in order to determine if they would fit into the space provided for housing of the species in the existing habitats on ISS.

Daily needs in dry food consumption, water intake, basal metabolic rate mlO2/g/h, body mass of adult, as well as the newborn weight, and environmental temperature were compared in order to determine whether the capacity of the habitats designed for mice and rats supports other rodents. Hair, feces, urine and food particles are by constant

**Table 2**
Taxonomy, body mass, head-body length, tail length, and life span in precocial rodents below 500 g body mass, rat and mouse.

| Common name | Species | Genus | Familiae | Body mass (g) | Head -Body length (cm) | Tail length (cm) | Life span (years) |
|---|---|---|---|---|---|---|---|
| Brown rat | *R. norvegicus* (Otto et al., 2015) | *Rattus* | *Muridae* | 250–500 | 25 | 20 | 2.5–3 |
| House mouse | *M. musculus* (Kingdon et al., 2013) | *Mus* | *Muridae* | 18–40 | 8.5 | 8 | 1–3 |
| Val's gundi | *Ctenodactylus vali* (George, 1978; George, 1982) | *Ctenodactylus* | *Ctenodactylidae* | 174 | 17.6 | 2.1 | ND |
| North African gundi | *Ctenodactylus gundi* (Brubaker and Coss, 2015-George, 1978) | *Ctenodactylus* | *Ctenodactylidae* | 200–350 | 208 | 2.9 | 6 |
| Mzab gundi | *Massoutiera mzabi* (Kingdon et al., 2013; George, 1978; George, 1988) | *Ctenodactylus* | *Ctenodactylidae* | 172–239 | 12.5–21 | 3.5 | ND |
| Speke's pectinator | *Pectinator spekei* (Nowak, 1999; George, 1978; Peters, 1871) | *Pectinator* | *Ctenodactylidae* | 178.2 | 16–19 | 5 | 4 |
| Felou gundi | *Felovia vali* (Kingdon et al., 2013; George, 1978) | *Felovia* | *Ctenodactylidae* | 185.8 | 16.9–19 | 7.3 | ND |
| Common degu | *Octodon degus* (Woods and Boraker, 1975; Ardiles et al., 2013) | *Octodon* | *Octodontidae* | 170–300 | 25–35 | 7.5–13 | 5–7 |
| Cairo spiny mouse | *Acomys cahirinus* (Haughton et al., 2016) | *Acomys* | *Muridae* | 30–50 | 9–13 | 9–13 | 7 |
| Eastern spiny mouse | *Acomys dimidiatus* (Kingdon et al., 2013) | *Acomys* | *Muridae* | 90 | 17.5 | 12.5 | ND |
| Common yellow-toothed cavy | *Galea musteloides* (Teta et al., 2009; Weigl, 2005) | *Galea* | *Caviidae* | 160–242 | 17.1–21 | tailless | 3.5 |
| Southern mountain cavy | *Microcavia australis* (Tognelli et al., 2001) | *Microcavia* | *Caviidae* | 200–326 | 17–24.5 | tailless | 8 |
| Long-tailed chinchilla | *Chinchilla lanigera* (Spotorno et al., 2004) | *Chincilla* | *Chinchillidae* | 422 | 26 | 13 | 10–20 |
| Dassie rat | *Petromus typicus* (Kingdon et al., 2013; Rathbun and Rathbun, 2006) | *Petromus* | *Petromuridae* | 111–286 | 13,5–22,4 | 11,6–17,5 | ND |

ND – no data; $X^{n}$ – number of reference.

**Table 3**
Existing variants of species (laboratory, domestic, wild), single or social housing, using sand baths and environmental temperature in precocial rodent species below 500 g body mass, rat and mouse.

| Common name | Species | Existing variants | Single/ Social | Sand baths | Environmental Temperature C° |
|---|---|---|---|---|---|
| Brown rat | *R. norvegicus* (Otto et al., 2015) | Laboratory, domestic, wild | Social | No | 18–24 |
| House mouse | *M. musculus* (Whary et al., 2015) | Laboratory, domestic, wild | Social | No | 20–23 |
| Val's gundi | *Ctenodactylus vali* (George, 1978; George, 1982) | Domestic, wild | Social | No | ND |
| North African gundi | *Ctenodactylus gundi* (George, 1982-Honigs and Greven, 2003) | Domestic, wild | Social | No | 22–27 |
| Mzab gundi | *Massoutiera mzabi* (Kingdon et al., 2013; George, 1978; George, 1988) | Domestic, wild | Social | No | ND |
| Speke's pectinator | *Pectinator spekei* (Nowak, 1999; George, 1978; Peters, 1871) | Domestic, wild | Social | No | 20–24 |
| Felou gundi | *Felovia vali* (Kingdon et al., 2013; George, 1978) | Domestic, wild | Social | No | ND |
| Common degu | *Octodon degus* ((Catlett, 1973)Woods and Boraker, 1975(Hagen et al., 2014); Ardiles et al., 2013) | Laboratory, domestic, wild | Social | Yes | 20–24 |
| Cairo spiny mouse | *Acomys cahirinus* (Haughton et al., 2016) | Laboratory, domestic, wild | Social | No | 21–26 |
| Eastern spiny mouse | *Acomys dimidiatus* (Kingdon et al., 2013) | Domestic, wild | Social | No | ND |
| Common yellow-toothed cavy | *Galea musteloides* (Teta et al., 2009; Weigl, 2005) | Domestic, wild | Social | No | ND |
| Southern mountain cavy | *Microcavia australis* (Tognelli et al., 2001) | Domestic, wild | Social | No | ND |
| Long-tailed chinchilla | *Chinchilla lanigera* (Spotorno et al., 2004) | Laboratory, domestic, wild | Single | Yes | 18–22 |
| Dassie rat | *Petromus typicus* (Kingdon et al., 2013; Rathbun and Rathbun, 2006) | Domestic, wild | Social | ND | 25 |

ND – no data; $X^{n}$ – number of reference.

airflow moved towards an exhaust filter in the rodent habitats. Daily fecal output, size of the feces droplets, urine output ml/24 h, and hair length were compared between the rodent species because of the possible differences which could disable cleaning of the air.

Data on the special hygiene habits, such as sand baths which are necessary for the fur cleaning in some rodent species were also registered. Creating a cloud of dust in microgravity could be dangerous because of inhalation of the small particles. On the other hand, not practicing sand baths will seriously compromise the health of animals.

For planning the timeline of the experiment and selection of the most promising species, data on their life span, length of the oestrus cycle, duration of pregnancy, data about their nest building, litter size, and duration of weaning is necessary.

Social characteristics of the animals regarding their keeping in a group or separately are important. A special problem is posed by the animals that are not domesticated, which were never in contact with people and this is the reason why it was examined whether domesticated precocial rodent species were identified, whether they were included into the research as laboratory animals or whether they were present only as wild animals. Regarding biohazard, it was examined whether they are known carriers, disease reservoirs.

Wild animals exhibit defensive behavior in response to a wider range and/or a weaker intensity of stimuli compared with domestic animals (Brubaker and Coss, 2015). Handling them could potentially be dangerous. Also, wild animals could be disease reservoirs. Because of that, World Wide Web was searched in order to find whether

**Table 4**
Characteristics related to air filtering, food, water, and oxygen provision in precocial rodents below 500 g body mass, rat and mouse.

| Common name | Species | Dry food consumption g/24h | Water intake ml/24h | Basal metabolic rate ml O2/g/h | Hair Length mm | Urine output ml/24h | Fecal output g/24h | Size of feces droplet mm |
|---|---|---|---|---|---|---|---|---|
| Brown rat | *R. norvegicus* (Otto et al., 2015; National Research Council (US) Subcommittee on Laboratory Animal Nutrition 1995—Chame, 2003) | 15 | 25–75 | 1.02±0.2 | 16 | 10–25 | 9–13 | 17 × 6 |
| House mouse | *M. musculus* (Whary et al., 2015; Chame, 2003) | 3–5 | 6–7 | 3.5 | 9 | 2.5* | 6–9 | 6 × 2 |
| Val's gundi | *Ctenodactylus vali* (George, 1982; Honigs and Greven, 2003) | ND | ND | ND | 17 | ND | ND | 8.9 ± 2.7 |
| North African gundi | *Ctenodactylus gundi* (Honigs and Greven, 2003; Honigs et al., 2002) | 10.8 | ND | ND | 17 | ND | ND | 9.62±0.5 |
| Mzab gundi | *Massoutiera mzabi* (George, 1988) | 5.5* | ND | ND | ND | ND | ND | ND |
| Speke's pectinator | *Pectinator spekei* | ND | ND | ND | ND | ND | ND | ND |
| Felou gundi | *Felovia vali* | ND | ND | ND | ND | ND | ND | ND |
| Common degu | *Octodon degus* (Kenagy et al., 1999-XXXX 2002) | 15.08±2.08 | 39* | 0.93 | ND | 14.5 ± 0.8 | 7.3 ± 0.91 | 7–8 × 3 |
| Cairo spiny mouse | *Acomys cahirinus* (Haughton et al., 2016; Dickinson et al., 2013(Czech and Vander Zanden, 1991)-Wise, 1977) | 5–6* | 7 | 0.64 | ND | 2* | ND | ND |
| Eastern spiny mouse | *Acomys dimidiatus* | ND | ND | ND | ND | ND | ND | ND |
| Common yellow-toothed cavy | *Galea musteloides* (Bellamy and Weir, 1972) | ND | ND | ND | ND | 18–24 | ND | ND |
| Southern mountain cavy | *Microcavia australis* (Sassi et al., 2010) | 20.98–29.24 | ND | ND | ND | ND | ND | ND |
| Long-tailed chinchilla | *Chinchilla lanigera* ((Poyraz et al., 2005) Spotorno et al., 2004; Donnelly and Brown, 2004-Busso et al., 2005(Wolf et al., 2003)) | 14.77* | 20–40 | 0.66 | 26 | 6.2 | 4.8 | 8,6 × 3,9 |
| Dassie rat | *Petromus typicus* ((George, 1981)Mess and Ade, 2005- (Scott and Cooremans, 1992) | 5.7 | 7.4–10.2 | ND | ND | ND | ND | 8 × 3 |

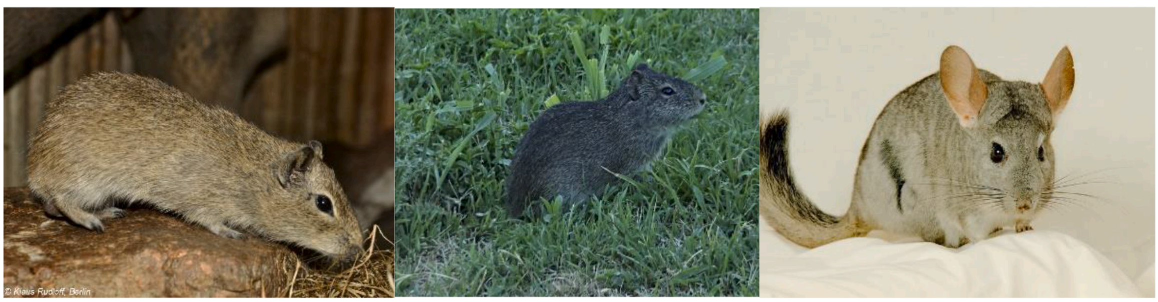
*Approximately calculated based on the given ratio in the references; ND – no data; $X^{n\,-}$ number of reference.

**Table 5**
Reproductive characteristics and musculoskeletal maturity at birth of precocial mammals below 500 g body mass, rat and mouse.

| Common name | Species | Musculoskeletal maturity | Length of oestrus cycle (days) | Duration of pregnancy (days) | Nest | Litter size | Newborn weight (g) | Weaning (week) |
|---|---|---|---|---|---|---|---|---|
| Brown rat | *R. norvegicus* (Otto et al., 2015) | Myotubular, primary ossification | 4–5 | 21–23 | Yes | 8–14 | 5–6 | 3 |
| House mouse | *M. musculus* (Whary et al., 2015) | Myotubular, primary ossification | 4–5 | 19–21 | Yes | 4–12 | 1–1.5 | 3 |
| Val's gundi | *Ctenodactylus vali* (George, 1978) | ND | 22 | 67 | No | 1–3 | 19.9 | ND |
| North African gundi | *Ctenodactylus gundi* (Rezende et al., 2004) | ND | 31 | 69–79 | No | 1–3 | 18–40 | 1 |
| Mzab gundi | *Massoutiera mzabi* (George, 1978) | ND | 26 | ND | ND | 1–3 | 20–21 | ND |
| Speke's pectinator | *Pectinator spekei* (Rezende et al., 2004) | ND | 25 | ND | ND | 1–2 | 19–20 | ND |
| Felou gundi | *Felovia vali* (George, 1978) | ND | 23 | ND | ND | 1–2 | ND | ND |
| Common degu | *Octodon degus* (Woods and Boraker, 1975; Mahoney et al., 2011-Reynolds and Wright, 1979) | ND | 21 | 90 | Yes | 6–10 | 14.6±.4 | 4–6 |
| Cairo spiny mouse | *Acomys cahirinus* (Haughton et al., 2016( Young, 1976); Brunjes, 1990-Dickinson et al., 2005) | Myotubular, primary ossification | 11 | 39 | No | 1–7 | 5.65±0.16 | 4 |
| Eastern spiny mouse | *Acomys dimidiatus* | ND | ND | ND | ND | ND | ND | ND |
| Common yellow-toothed cavy | *Galea musteloides* (Rood and Weir, 1970-Eisenberg and Redford, 1999) | ND | 22.3 ± 1.4 | 52–54 | No | 1–5 | 36.4–37.6 | 3 |
| Southern mountain cavy | *Microcavia australis* (Tognelli et al., 2001; Rood and Weir, 1970; Keil et al., 1999) | ND | 15 | 53–55 | No* | 1–5 | 17–44 | 3 |
| Long-tailed chinchilla | *Chinchilla lanigera* (Donnelly and Brown, 2004; Dzierzanovska-Goryn et al., 2014) | ND | 39 | 111 | No | 1–6 | 49.5 | 6–8 |
| Dassie rat | *Petromus typicus* ((Coetzee, 2002)Mess, 2007-Rathbun and Rathbun, 2009) | ND | ND | 84–91 | No | 1–3 | 10.5–20 | 3 |

* Semi-fossorial animal; ND – no data; $X^n$ number of reference;.

*Mus musculus* (mouse) | *Ratus norvegicus* (rat) | *Acomys dimidiatus* (spiny mouse)



*Galea musteloides* (common yellow-toothed cavy) | *Microcavia australis* (southern mountain cavy) | *Chinchilla lanigera* (long-tailed chinchilla)

*Ctenodactylus gundi* (common gundi) | *Petromus typicus* (dassie rat) | *Octodon degus* (common degu)

**Image 1.** Altricial and precocial rodents.

domesticated (farming, zoo, pet animals) exist or not, and laboratory precocial rodent species which were previously selected.

Data about: adult body mass, newborn body mass, head-body length, tail length, existing variants (wild, domesticated, laboratory), single or in group housing, dry food consumption/24 h, water intake/24 h, basal metabolic rate mlO2/g/h, environmental temperature, sand baths, urine output ml/24 h, fecal output g/24 h, size of fecal droplet, hair length, life span, length of oestrus cycle, duration of pregnancy, building nest, litter size, stage of musculoskeletal maturity, and the duration of weaning was obtained by searching SCOPUS as well as the World Wide Web with key words for each of the species in English, Latin and, where possible, by the local language name. These characteristics were compared in order to find most appropriate species.

## Results

Forty precocial rodent species were identified from 28 genera and 16 families. This number is not final because only genus *Acomys* has 19 species of which available data suggest that two species belong to the precocial rodents while for 17 species data are missing. Species with a bodyweight greater than the weight of *R. norvegicus*, 28 of them, are shown in Table 1.

Twelve precocial rodent species were identified with body mass of 500 g (Table 2). They are all available as domesticated animals (zoo) and three of them as laboratory animals (Table 3).

Some literature data described housing of gundis (*Ctenodactylus gundi* or comb rats) in zoo conditions, in a terrarium, as well as in laboratory conditions. Although they clean their fur with toe bristles, gundis also use fine sand for coat care (Karen, 2005). Terrariums could reproduce natural sunbathing places (stones that were heated up to 30 °C daily). It is interesting to note that they appear fully weaned after few days (Karen, 2005). Some data suggest that in laboratory conditions, these social animals were housed and reproduced for eight years without sand bath and sunbath (Karen, 2005). The staff responsible for

*Ctenodactylus gundi* in the zoo describe the appropriate husbandry as too complicated (personal communication with Sandra Honigs, Curator responsible for husbandry of *Ctenodactylus gundi* in the Dusseldorf Zoo in Germany). Only a couple of people have gundis as a pet in Europe. On the internet they posted that, if gundis are handled with enough care, they can be a good pet. They are considered to be highly intelligent and like to remain occupied. Gloves are not recommended. They have a constant need for chewing things ((ZZZZ 2000) (ZZZZ 2000)). They represent a natural resorvoir for Leishmaniasis, 40% of gundies are possitive to Leishmaniasis (Ghawar et al., 2018). This species were prone to infection with *Toxoplasma gondii* (Honigs and Greven, 2003).

*Octodon degus* is a social animal that adapts well to most laboratory conditions, and it could be a pet animal as well. A daily sand baths is necessary for fur and skin hygiene. Hand rearing is possible; gloves are not needed, and, like chinchilla with improper handling, it could lose its tail (Woods and Boraker, 1975). The number of fetuses in the first gestation may be lower than in subsequent pregnancies. The first litter of an *Octodon degus* typically contains 4–6 newborns, while subsequent litters have 6–10 newborns (Ebensperger et al., 2007). Although *degu* is a precocial species, literature data suggest that newborns remain in the nesting site for approximately two weeks (Ebensperger et al., 2007). This rodent has a natural resistance to insulin. It has a strong predisposition to diabetes mellitus when fed a carbohydrates rich diet (a model in comparative biology and biomedicine) (Woods and Boraker, 1975).

It is possible to keep a spiny mouse (genus *Acomys*) in typical mouse and rat enclosure. In contrast to rats and mice, they have a strong need to be housed in a group. Also, they are very curious and like to explore their environment, so they need complex surroundings (Haughton et al., 2016). It is a pet animal, usually friendly species. Hand-rearing is possible, gloves are not required. They are also agile and can become excited quickly. If the spiny mouse is improperly handled, it could struggle vigorously, losing its tail or strips of skin up to 60% on its back, leaving large wounds (Haughton et al., 2016). The tensile strength of laboratory mouse skin is 21 times greater than the tensile strength of the spiny mouse (Haughton et al., 2016). Healing of the wounds happens quickly in a couple of days (Haughton et al., 2016). *Acomys caharinus* is prone to obesity and diabetes mellitus in captivity (Haughton et al., 2016). The data about the musculoskeletal maturity for the newborn period are only available for *Acomys caharinus*. The bones of this species are at the initial ossification stage (Niedzwiedz et al., 1999), while muscles are in the myotubular stage (Oron et al., 1988). For other precocial rodents mentioned in Table 2, a search of the literature about muscle and bone maturity at birth did not reveal any information. Data about Eastern spiny mouse is missing except for physical characteristics. Data for *Microcavia australis* and *Galea musteloids* species is limited. *Microcavia australis* is a semi-fossorial animal. It digs tunnels in which it hides. Details regarding its breeding or keeping as a pet animal could not be found. Regarding behavior, both species are social (Tognelli et al., 2001; Keil et al., 1999; Eisenberg and Redford, 1999). Published articles do not describe demands for anesthesia of wild *Microcavia australis* specimens during experimental manipulation (Andino et al., 2011). Anecdotal information from World Wide Web shows that *Microcavia australis* is not afraid of humans; it lives in house backyards. *Microcavia australis* could be recovered after injury under human care and could easily breed as pet animals. It is not known that *Microcavia australis* is diseases reservoir nor transmit diseases to humans. This species is widely used in Ecuador as a food source ((ZZZZ 2001) (ZZZZ 2001)). However, both *Galea musteloids* as well as *Microcavia australis* belong to the same family as *Cavia porcellus*, a well-known laboratory animal. Considering that they could potentially be good candidates for future microgravity experiments and may have similar characteristics to *Cavia porcellus*, the features of *Cavia porcellus* should be further mentioned. The food consumption is 6 g/100 g body weight/day, while the oxygen consumption rate is 0.76–0.83 ml/g body weight/h (Shomer et al., 2015). Available data suggest that water consumption is 10 ml/100 g body weight/day. Urine output is 4–9 ml/100 g bodyweight and daily fecal output 15–18 g (Shomer et al., 2015). Hair length is 10–25 mm (Dawson, 1930). The specificity of this species is the absence of L-gulonolactone oxidase necessary for the synthesis of vitamin C, so daily supplementation with 10 mg of Vitamin C / kg body weight is needed. Humans, as well as the rest of *Haplorrhini*, a suborder of primates, also lack L-gulonolactone oxidase (Donnelly and Brown, 2004). Data related to the eventual lack of L-gulonolactone oxidase in *Microcavia* or *Galea* could not be identified in the literature. Guinea pigs often develop pregnancy toxemia in late pregnancy. Metabolic toxemia develops in obese sows when they reduce carbohydrate intake and mobilize fat as a source of energy, which causes ketoacidosis. The circulatory toxemia is due to uteroplacental ischemia. The gravid uterus compresses the aorta, resulting in a significant reduction of blood flow to the uterine vessels (Donnelly and Brown, 2004). There is no data in the literature that *Microcavia* and *Galea* are also prone to toxemia during gestation. It should be noted that *Cavia porcellus* represents one of the significant sources of meat in South America because of easy breeding (Donnelly and Brown, 2004).

*Chinchilla lanigera* is housed as a single individual. They are nervous, shy animals could be easily distressed, and need a place to hide when in captivity. It is a pet animal, it could be hand-reared, gloves are not recommended, but even well-treated chinchillas could bite if frightened. Improper handling could result in spraying urine on enemies at a distance of up to 75 cm. It could also lose a patch of fur (fur-slip) or tail if they grabbed inadequately. Housing this species like *Octodon degus* also demands a daily sand baths. This species was intensively commercially bred because of its fur (Donnelly and Brown, 2004).

There is not much data about *Petromus typicus*. It is a social rodent, which lives in small family communities, but it could be housed as a single animal as well. They were offered sand baths in captivity, but it is not clear whether they practiced them (Mess and Ade, 2005). This species is extremely difficult to maintain in the laboratory (Withers et al., 1980). It is even difficult to obtain precise information about vaginal closure membrane as a daily routine (Mess, 2007).

## Discussion

Presented data shows that demands in available space, environmental temperature, daily oxygen supply, water, and food needs for precocial rodents could be managed with Rodent Habitat (USA) on the ISS. Contaminants produced with precocial experimental animals such as urine, fecal particles, hair, and carbon dioxide are also similar to contaminants from rats, and the same atmospheric filtering unit could eliminate them.

Although gundis may be kept as pet animals, they are a more demanding species for appropriate tending. Litter size is small, which makes them a less suitable species for experiments in microgravity on board ISS. *Octodon degus* requires sand baths as well as a nest during the first two weeks after delivery, which is why this species is not suitable for experiments in microgravity. Separate keeping of the spiny mouse species within the experiment with delivery in the microgravity conditions is not appropriate because they are an extremely sociable species. The experiment with gravid animals kept together before the delivery term is possible. Muscle maturity of this species at birth, which is in myotubular stage (Brunjes, 1990), does not correspond to the stage of human muscle development at birth - late histochemical stage (Sekulic et al., 2006). Considering already difficult extrapolation between species, when it comes to different maturity stages, makes this extrapolation even more complicated. Using this species in experiments that involve reproduction in altered gravitational conditions could provide basic knowledge about effect of microgravity of mammal's prenatal development, but, it should not be used as a translational model for examining the effects of microgravity on human species. For *Galea musteloides* and *Microcavia australis* there are no data regarding environmental temperature, hair length, urine output, fecal output, size of feces droplets, dry food consumption, water intake, basal metabolic rate ml O2.

Considering the fact that in comparison with rats, other precocial rodent species from Table 4 Table 5. have the same or lower values, it can be assumed that rodent habitat supports in air filtering and housing of *Galea musteloides* and *Microcavia australis*. Possibility of keeping *Microcavia australis* as pet animal, short estrus, large litter size, absence of the need for nest and sand baths makes this species the most promising candidates for experiments on ISS. Chinchilla species requires that each animal is housed separately, which is not feasible now on ISS because of absence of such habitats. Taking into consideration that the Rodent Habitat anticipates the rats weighing 250 g, chinchillas do not fulfill the conditions. They also require daily sand baths, for which there are no conditions on ISS. According to physical characteristics, food and water consumption, absence of the need for sand baths and making nests, Dassie rat provides the possibility for experiments on board ISS. However, it is extremely difficult to maintain in laboratory this species and because of that it is not an adequate for experiments on ISS.

If an experiment is planned with exposing gravid animals before term of the birth, then they might be kept together in the existing Rodent Habitat (USA). If an experiment with birth is planned in microgravity on ISS, the existing habitats do not provide conditions for such an experiment. It is necessary to develop habitats for separate keeping of pregnant animals in order to enable following: 1. undisturbed delivery 2. prevent the possibility of hurting the newborns 3. ensure adequate post-partum maternal care and nursing (Ronca et al., 2013)

The possible lifespan of the ISS is expected until at least 2030 which give enough time to examine the reproductive possibilities and characteristics of precocious rodents in laboratory conditions on Earth. Usage of gloves on ISS demands a check of their resilience to bites or chews for new experimental species. As part of a selection of species, pregnant animals should be exposed to short term hypergravity but also vibrations (van Loon, 2016; de Sousa et al., 2020), which correspond to conditions during the launch of the applied rocket systems – a Launch Simulation Test. It is necessary to identify species that could withstand, in pregnant conditions, launch characteristics of particular rockets used for such experiments. Next, rodent habitat biocompatibility tests should be performed to determine possibility and length of time the habitat could support that particular experimental animal (Wade, 2005). Instead of performing a study using a full length gestation in microgravity, the first step could be to repeat the strategy to send already pregnant animals and keep them exposed to microgravity until the last days of gestation (Ronca, 2003). Before the launch, by using ultrasound or microscopic magnetic resonance examination in a noninvasive manner (short term anesthesia), experimental animals with a desirable number of fetuses could be selected. In this way, pregnant animals with more fetuses and also without congenital malformation/deformation could be used. Also, it could be possible in this way to track eventual resorption of fetuses. The next step could be a mission with experiments of reproduction/birth of first mammals in space. Logistics, especially the lengthy interval between reentry and recovery could significantly affect study findings (Ronca, 2003; Choi et al., 2020). Conversely a minus eighty deggree Laboratory Freezer for sample storage exclude interval between reentry and sample recovery with period of ambulation of experimental animals prior to recovery (Cheganças et al., 2007).

Excluding *Acomys cahirinus,* all other precocial species from Table 2 are lacking description of bone and muscle development at birth. It will be necessary during preflight preparation to fill this gap in knowledge.

Order *Rodentia* is not the only the mammalian order with lightweight precocial species. For example *Elephantulus rufescens* are precocial mammals, order *Macroscelidea*, with an adult average weight of 58 g, a body length 255.3 mm, and tail length 133.3 mm (Koontz and Roeper, 1983). Gestation length 57–65 days, only singleton and twin births were recorded. Elephant shrews are shy and tend to stay away from anything they perceive as a danger. It might be important to consider their sensitivity for noise and good acoustic shielding (Koontz and Roeper, 1983). Choosing between precocial animals largely depends on the objectives of the experiment (fetal development/birth of precocial mammals in microgravity or precocial rodent species), available launch systems, rodent habitats, and species limitations.

Further experiments on the ISS with precocial rodent species could give additional data about mammalian prenatal development in microgravity. If the structural or any irreversible changes of the fetus's physiology and development in experimental animals are to be discovered, then the physiological development of human fetuses in microgravity is not possible. To counteract the effects of microgravity, astronauts regularly exercise on daily basis, during flight, but the fetus cannot exercise like an astronaut (Denisova, 1986). Considering the principle that the larger the animal, the more pronounced the effect of the altered gravitational regime is (Wade, 2005), and that rodent fetuses are significantly lighter than human fetus, it should be expected that changes in human fetus would be more pronounced. If this would be the case, microgravity would be a showstopper for prenatal development, and further design of spaceships, orbital stations, and permanent bases on other celestial bodies must include a centrifuge to make colonization of solar system possible (Hall, 2020; Young et al., 2006; van Loon et al., 2012). Exposing humans to a well-known harmful factor, such as microgravity, raises ethical issue as well. Career space workers as well as future space tourists should be provided with adequate levels of gravity in order to mitigate or completely abolish the microgravity-related pathologies we currently see (van Loon et al., 2020).

## Contributions

S.S., A.J., Z.Z, S.S., S.K., B.P. and I.C.: Literature review and manuscript writing; S.S. and J.J.W.A.L: Manuscript writing and editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that cdocould have appeared to influence the work reported in this paper.

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