REVIEW

A Scientific Review of Age Determination for a Laboratory Rat: How Old is it in Comparison with Human Age?

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ABSTRACT

Laboratory rats are among the most commonly used experimental animals, offering the best functionally characterized model mammalian system. The rat serves as a model organism for the analysis of a number of important biomedical traits, including toxicology. In many instances, while individuals engaged in research are calculating doses for an experiment or relating the health effect of a certain drug or chemical to a human, questions arise such as 'how old is a rat in people years?' or 'is a newborn rat a good model for a newborn human?'. Some reviews have tried to answer these questions in various ways. This review attempts to answer such questions using a different approach, and shows that rat-human age correlations differ markedly at different stages of life and development. This review metaphorically illustrates the correlation of their different age periods, from the weaning (where 42.4 rat days resemble a human year) to aged phase of life (where 17.1 rat days equal a human year). Biomed. Int. 2011; 2: 81-89. ©2011 Biomedicine International, Inc.

Key words: Age; laboratory; human; rat

INTRODUCTION

The use of laboratory animals, including the rat, continues to be an important part of biomedical research. Rats have been used in scientific research since the 1600s. However, the development of the laboratory rat as a research model really began in 1906 when the Wistar Institute developed the Wistar rat model (Rattus norvegicus) for biological and medical research. Today, the laboratory rat is recognized as the preeminent model for research into various areas, including cardiovascular disease, neurological disorders, neurobehavioral studies, cancer susceptibility and renal disease. They are prized for many qualities since a large number can be reared in a short time with the minimum of expense and with ease of breeding within the laboratory.

Rats in biomedical research: a historical outlook

Rats are thought to have originated in the area of Asia currently occupied by southern Russia and northern China (Figure 1). Rattus rattus (2n = 38) was well established in Europe by 1100 A.D. (following the Crusades), with Rattus norvegicus (brown rat, 2n = 42) commonly found in Europe in the 1700s. This recent reappearance followed thousands of years of absence. Fossilized rat remains dating to the Pliocene and Pleistocene periods have been found in Europe. Until the writings of Giraldus Cambrensis (1147–1223), there was...
no distinction between *R. rattus* and mice. The late arrival of *R. norvegicus* in Europe was offset by its ferocious nature, essentially eradicating the black rat from its former strongholds. Today, the black rat is restricted to areas near water, and the brown rat has conquered the planet because of its climatic adaptability and ability to co-exist with human refuse. Today’s laboratory rats are the domesticated descendants of *Rattus norvegicus*. Albino animals were held and used for rat shows, and frequent handling is thought to have tamed them. By the 1800s these animals were used for breeding and for neuroanatomy studies in the United States and Europe. It was in the late 1800s and early 1900s that individual stocks and strains had their beginnings. The laboratory rat has been, and continues to be, a mainstay of biomedical research. Both albino and pigmented animals are available. There are recognized differences between wild and laboratory rodents. For example, laboratory rats have smaller adrenals and preputial glands, earlier sexual maturity, no reproductive cycle seasonability, better fecundity, and a shorter lifespan than their free-ranging wild counterparts.³

RAT AGE VERSUS HUMAN AGE: COMPARING DIFFERENT STAGES OF LIFE

Researchers in pharmacology, toxicology, or any biomedical science that uses rats as an experimental model, often face problems such as the question of ‘how to correlate the result of an experiment found in pubertal or aged rat with a human’, or, while calculating doses for an experiment for a certain drug or chemical in a rat model, ‘how old is a rat in people years?’. Very few previous research studies and reviews have attempted to answer these questions. Some experiments have been carried out using the weight of the eye lens⁴ in an attempt to use the development and growth of the lens throughout mammalian life as an indicator that could help to correlate the ages of different species.⁵ This technique was taken as a useful measure in the late 1980s to correlate the ages of different mammalian species at different stages of life. However, this method proved a useful indicator only up to three to four months; beyond that point, the technique is not precise enough to determine the exact age of the rat. Subsequently, some researchers developed
methods to determine the ages of smaller mammals by using the growth of molar teeth. Some reports have also suggested counting endosteal layers in the tibia to correlate the ages of small mammals with that of a human. However, in this review, a different approach has been taken to correlate rat with human age.

**Entire life span**

Domestic rats live approximately 2 to 3.5 years. In a survey of pet rat lifespan in the UK, the average lifespan was 21.6 months, and 95% died by the age of three years. In contrast, 95% of rats living in the wild die before 1 year of age. While the worldwide life expectancy of humans is 66.7 years, it varies a great deal among different countries. Human lifespan tends to correlate with economic development: people in the 55 most developed nations have average life-spans of 77.1-80 years, while people in the 33 least developed countries have average life-spans of 49.4 years. In 2003, Japan had the highest life expectancy at 81.3 years, while Zambia had the lowest, 33.4 years. Table 1 shows life span, body weight, developmental and reproductive events of the laboratory rat.

<table>
<thead>
<tr>
<th>Life span</th>
<th>Captivity</th>
<th>2-3.5 years</th>
<th>Pass and Freeth, 1993⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td>Birth</td>
<td>5-6 g</td>
<td>Pass and Freeth, 1993⁸</td>
</tr>
<tr>
<td></td>
<td>Weaning</td>
<td>30-55 g</td>
<td>Pass and Freeth, 1993⁸</td>
</tr>
<tr>
<td></td>
<td>Puberty</td>
<td>150-200 g</td>
<td>Pass and Freeth, 1993⁸</td>
</tr>
<tr>
<td></td>
<td>At 12 weeks: males</td>
<td>200-400 g</td>
<td>Pass and Freeth, 1993⁸</td>
</tr>
<tr>
<td></td>
<td>At 12 weeks: females</td>
<td>150-270 g</td>
<td>Pass and Freeth, 1993⁸</td>
</tr>
<tr>
<td></td>
<td>Adult: males</td>
<td>300-800 g</td>
<td>Pass and Freeth, 1993⁸</td>
</tr>
<tr>
<td></td>
<td>Adult: females</td>
<td>Adult: females</td>
<td>Pass and Freeth, 1993⁸</td>
</tr>
</tbody>
</table>

**Developmental and reproductive events**

| Puberty: males | 39-47 days | Engelbregt et al., 2000¹¹; Chappel and Ramaley, 1985¹²; Korenbrot et al., 1977¹³ |
| Puberty: females | 34-38 days | Engelbregt et al., 2000¹¹ |
| Social maturity | 160-180 days (5-6 months) | Adams and Boice, 1983¹⁴ |
| Estrus cycle | 4-6 days | Pass and Freeth, 1993⁸ |
| Gestation | 21-22 days | Pass and Freeth, 1993⁸ |
| Menopause (females) | 450-540 days | Durbin, 1966¹⁵ |

Individuals performing research using the rat model often ask questions such as: “How many ‘rat days’ equal a ‘human year’?” “When are these animals considered ‘adult’ or ‘aged’?” The easiest way to approach this is to make a simple direct comparison between the life spans of the two species, such as: the average laboratory rat lives approximately three years and the average human lives approximately 80 years. So, (80×365) ÷ (3×365) = 26.7 human days = 1 rat day; and, 365+26.7 = 13.8 rat days = 1 human year. It seems an easy calculation, but does it fit with each stage of a rat’s life?

**Birth and childhood**

The birth weight of a newborn rat is approximately 5 to 6 g. The average adult male weight of a Sprague-Dawley rat fed ad libitum levels off at about 550 g (Figure 2).
Therefore, a rat’s birth weight is approximately 1% of its adult weight. Human birth weight averages around 2.7 kg. The average adult male human weight is around 82 kg. Therefore, human birth weight is approximately 3% of adult weight. Romijn et al. used a variety of measurements and determined that the cerebral cortex of a newborn human is developmentally most comparable to that of a 12- to 13-day old rat pup. If one considers the birth weight comparison, a 12-day-old rat pup will weigh approximately 20 g, which corresponds to 3.6% of its adult weight. Therefore, it can be concluded that one should not even consider the rat “born” until postpartum day 12. Its first 12 days of postnatal life are probably comparable to the late gestational period in humans. On this assumption, 12 days should be deducted from the rat’s life span, corresponding to 1% of its total life span; therefore, the calculation above should be adjusted and the “true” conversion rate becomes 13.8 rat days=1 human year.

Weaning

Weaning is the process of gradually introducing a mammalian infant to what will be its adult diet and withdrawing the supply of its mother’s milk. In the United States, the average weaning age for humans is approximately 6 months. In most laboratory scenarios, the weaning age is usually set at 3 weeks for rats and mice. As long as the only comparison being made is the age at which they stop receiving maternal milk, the comparison is reasonably meaningful. It has been already mentioned that the rat is not officially “born” until day 12; therefore, nine days elapse between the time it is developmentally similar to a human newborn and the time it is weaned. The calculation can now be modified using only the period of “birth” to “weaning”. Rats are weaned at nine days after “birth”, and humans are weaned at (6×30) 180 days after birth. Thus, 180÷9 = 20 human days=1 rat day, and, 365÷20 = 18.3 rat days=1 human year. This is correct when the times that the “infant” is consuming maternal milk are compared; these times must be counted from the day of delivery because newborns start nursing almost immediately. Therefore, rats are weaned at 21 days after birth and humans are weaned at...
(6×30) 180 d after birth. Thus, 180÷21 = 8.6 human days = 1 rat day and 365÷8.6 = 42.4 rat days = 1 human year.\textsuperscript{16}

Reproductive functions

Research on the reproductive physiology of the rat as an experimental animal began in the 1930s. Since then, the species has been more thoroughly characterized in these research fields than any other laboratory animal model.\textsuperscript{22,23} There are many differences in reproductive physiology between the rat and the human, which must be taken into account when the reproductive ages of the two species are compared (Table 2).\textsuperscript{24,25}

<table>
<thead>
<tr>
<th>Table 2. Differences in the reproductive functions of the rat and the human.</th>
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<tbody>
<tr>
<td>Reproductive strategy of the rat differs from that of the human:</td>
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<tr>
<td>1. The rat is a short (22.5 day) gestation species. Pregnancy in humans is 9 months.</td>
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<td>2. In the rat, sexual differentiation of the reproductive tract is perinatal, whereas for the central nervous system (CNS) sexual differentiation is a postnatal event, regulated to a great degree by the aromatization of testosterone to estradiol (play behavior, an exception, is androgen-dependent in both rats\textsuperscript{26,27} and humans\textsuperscript{28}).</td>
</tr>
<tr>
<td>3. In non-human primates and presumably humans, more CNS events are prenatal, and androgens are more important than in rats.\textsuperscript{28-31}</td>
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<td>4. The rat has a 4- to 5-day estrous cycle, with no functional corpora lutea. The female rat displays sexual receptivity only during estrus after “lights out” after a proestrus vaginal smear. This behavior is exquisitely dependent upon estrogen followed by progesterone. Humans have a menstrual cycle approximately 28 days in duration and do not display periods of peak behavioral estrus during the cycle. Corpora lutea function is sustained for approximately 10 days by mating-induced cervical stimulatory prolactin surges in rats, whereas the human menstrual cycle has a spontaneous luteal phase of 10 to 14 days after ovulation.</td>
</tr>
<tr>
<td>5. Male rat sexual behavior can be induced by estrogens and involves multiple series of ejaculations in a single mating. Mating involves approximately 10 mounts, with intromission before each ejaculation, followed by a post-ejaculatory interval before the onset of the next series. In nonhuman primates and presumably humans, male sex behavior is androgen mediated.</td>
</tr>
<tr>
<td>6. Both ovaries spontaneously release several ova in response to a luteinizing hormone surge into separate uterine horns, each with a separate cervix in the rat; whereas in women, a single ovum is typically ovulated during each cycle.</td>
</tr>
<tr>
<td>7. Spermatogenesis begins at approximately 5 days of age in the rat; the spermatogenic cycle is about 53 days, and sperm appear in the epididymis at about 55 days of age. In humans, spermatogenesis begins during puberty at 10 to 14 yr of age, and the entire spermatogenic cycle is approximately 75 days in duration.</td>
</tr>
<tr>
<td>8. Puberty in the rat (as measured by the age at vaginal opening and the onset of estrous cyclicity) occurs at about 32 days of age in females and 42 days of age (as measured by preputial separation an androgen-dependent event) in male SD and LE rat strains. In humans, puberty occurs at 9 to 12 yr of age in girls, and 10 to 14 yr of age in boys.</td>
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<tr>
<td>9. Fertility begins to decline in the female rat at about 6 months, especially if never mated and allowed to cycle continuously. Fertility begins to decline in women at about 35 yr of age, and at 40 yr of age, approximately 50% of women are infertile.</td>
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Puberty

Puberty is the time when reproduction is first possible, i.e. when germ cells are released. Vaginal opening, changes in vaginal smear, sexual receptivity and ovulation are integral factors in the attainment of puberty by the female rat. Compared to humans, rats have a brief, accelerated childhood, but the age of puberty in rats is quite variable. Some pioneering research was carried out in the early 1900s to determine exact age at which a rat
attained puberty. Long and Evans\textsuperscript{32} found that rats reached puberty at an average age of 76.5 days, with a range from 53 to 142 days. Freudenberger\textsuperscript{33} stated that the Wistar strain attained puberty at 46.9 days after birth, with a range from 36 to 66 days. In his own laboratory the rats reached puberty at 52.7 days with a range of 39 to 101 days. Slonaker\textsuperscript{34} gave the average age of pubescence in his strain as 80.6 days. At Cornell, the average age at the time of vaginal opening of different groups of intact normal rats was between 58.6 to 61.1 days.\textsuperscript{35} There remained widespread differences in these reports. However, the differences were resolved in the late 1900s: rats develop rapidly during infancy and become sexually mature at about 6 weeks, or at 40 to 60 days.\textsuperscript{36} Humans, on the other hand, develop slowly and do not reach puberty until about age 12-13 years (range: 8 to 16 years). Although rats become sexually mature at 6 weeks, they reach social maturity several months later, at about 5 to 6 months.\textsuperscript{14} In adulthood, each rat month is roughly equivalent to 2.5 human years\textsuperscript{37}, with 50 days taken as a reasonable average for our comparison. Humans reach sexual maturity at approximately 11.5 y on average.\textsuperscript{38} The gives us an indication of how we can compare the periods from the actual time of birth to the time when the individual can conceive. From, this, rats reach sexual maturity at approximately 50 days old while humans reach sexual maturity at approximately (11.5×365 =) 4198 days old. Thus, \(\text{4198÷50 = 84.0 human days=1 rat day.} \) Therefore, \(\text{365÷84.0 = 4.3 rat days=1 human year.} \) However, as has already been mentioned, rats are not “born” until day 12. This means that rats reach sexual maturity at approximately 38 d (50-12), while and humans reach sexual maturity at approximately 4198 d of age (11.5×365). Thus, \(\text{4198÷38 = 110.5 human days=1 rat day and 365÷110.5 = 3.3 rat days=1 human year.}\)\textsuperscript{16}

\textbf{Adulthood}

To identify adulthood by musculoskeletal maturity in rats is problematical as there is no epiphyseal closure in the long bones.\textsuperscript{39} At approximately 7 to 8 months of age, skeletal growth tapers off in male and female Sprague-Dawley rats.\textsuperscript{18} In humans, growth plate closure is rather inconsistent among individuals and between different growth plates within the body. One of the last growth plates to fuse is in the scapula, which closes at about 20 years of age on average\textsuperscript{40}; therefore, rats reach a “mature” skeletal size by 210 days (30×7) while humans reach total skeletal maturity at approximately 7300 days (365×20). Thus, \(\text{7300÷210 = 34.8 human days=1 rat day.} \) This would indicate that \(\text{365÷34.8 = 10.5 rat days=1 human year.}\)\textsuperscript{16}

\textbf{Reproductive senescence and post senescence}

In this review, only female senescence will be taken into consideration because male senescence appears to be highly variable among both rats and humans. According to Meites\textsuperscript{41}, reproductive senescence in female rats occurs between 15 and 24 months of age. According to the American Medical Association, the average age of menopause in women is 51 years (ranging between 48 and 55 years)\textsuperscript{42} and female rats enter menopause between ages 15 and 18 months.\textsuperscript{15} Therefore, female rats reach reproductive senescence at 600 days (20×30) and female humans reach reproductive senescence at 18615 days (51×365). Thus, \(\text{18615÷600 = 31.0 human days=1 rat day, and, 365÷31 = 11.8 rat days=1 human year.} \)\textsuperscript{16} If the periods from post-senescence to death are compared, the following is found: female rats live an average of 485 days ([365×3]-600) after senescence and female humans live an average of 10585 days ([365×80]-18615) after senescence. Thus, \(\text{10585÷495 = 21.4 human days=1 rat day, meaning 365÷21.4 = 17.1 rat days=1 human year.}\)\textsuperscript{16}
ANSWERING THE QUESTION: ‘How old is a rat in people years?’

If all of the above analyses are given equal consideration and if the actual parturition time is taken as the 'birth' for both species, the average age rate conversion would be as follows:

- **Total lifespan:** 13.8 rat days = 1 human year;
- **Weaning period:** 42.4 rat days = 1 human year;
- **Prepubescent period:** 3.3 rat days = 1 human year;
- **Adolescent period:** 10.5 rat days = 1 human year;
- **Adult phase:** 11.8 rat days = 1 human year;
- **Aged phase:** 17.1 rat days = 1 human year;
- **Average:** 16.4 rat days = 1 human year.

It is evident that comparisons made in the very early phases of life will be drastically different from those made in later adulthood. Thus, for example, to study neurobiological changes associated with bariatric surgery in an obese rat model, one would have to look at changes in 10- to 12-week-old animals. In this case a conversion rate of approximately 10 to 12 rat days per human year would probably be appropriate. Quite the reverse would occur if one was studying mammary gland developmental changes in association with diet and looking at gland development from 3 to 7 weeks of age, when a conversion of approximately 4 rat days per human year would probably be more reliable.

**CONCLUSION**

In a nutshell, this review provides a detailed comparison between rat and human age at different stages of life. It also suggests that rats, which are the most preeminent animal model in biomedical research, should not be viewed as miniature people, i.e. the three years a rat lives are not directly equivalent to a miniature form of human life. Differences in physiology and development must be taken into consideration when the results of any experiment in which age is a decisive factor are correlated with a human perspective. It is important for a researcher to understand that the relative ages are different depending upon the stage of life, so one has to determine the relevant age under investigation, and what factors are being analyzed.

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