Genome similarity among Rodentia and Homo sapiens, and scientific rationale for why rodents are regularly subjected to experimentation

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Abstract: Rodentia, exclusively rats, are often scrutinized by humans as a pest that is filthy, greedy, and spreads diseases. Rats actually share a variety of similarities with humans in internal structure, sociality, and behavior. This is a result of the rat genome closely resembling the genome of humans. Yet, rats have very different clades compared to homo sapiens. The similarities in genome along with other structural and behavioral reasons, have led to scientists using laboratory rats as research models for lab experiments. Along with referencing several research experiments, the review a selection of discoveries that furthered our comprehension of fields such as psychology, bio-medicine, mammalian evolution, and social behavior. In conclusion, the paper explains the reasons behind why rodents are tested, and how testing has helped us better understand not only rats but also the human specie in more detail, while analyzing limitations to rat experimentation.

Introduction

The rationale behind the review paper is to understand genomic similarities among rats and humans. Rats and mice are used by researchers (95%) to perform scientific

experiments (BR 2010). The rat is primarily known as a physiological model. Rat experimentation has led to novel findings in the fields of genetics, pathology, pharmaceuticals, human biology, psychological research, group behavior and overcrowding (Bethesda 2004). The major reason is because of the similarities of the genome of a rat and the human genome (Bethesda 2004). A comparison of gene sequence of rats, mice, and humans has lead to a new understanding of mammalian evolution. The goal being to fight human diseases and to do a comparison of its genome to the human genome (Zerhouni 2004). Scientists have been able to compare genomes of the three species to better understand human biology. The application and reaction of new medicine may elicit different responses from rats than humans, which is why, after successful testing, the medicine is then tested on more complex animals such as apes. Rats tend to be the first research model because of their size and its inexpensiveness, compared to primate testing. Along with there not being a direct translation of effects on rats and humans, researchers have to also follow regulations in order to legally complete an experiment, and they are oftentimes subject to3 possible scrutiny from public groups and/or individuals for unethical experimentation.

Methods and Materials

The comparison of the three genomes revealed similarities in large chromosomal regions. The comparison was made possible by the Rat Genome Project, which produced a high-quality draft of the Norway rat sequence. The project covered over

90% of its genome. The regions of similarity between the rats, mice and humans, were inherited with little rearrangement of gene order. The intact regions were inherited by a descendent of the primate-rodent ancestry. Since the separation of primate and murid, and the separation of rat and mouse, the orthologous regions have interspersed by chromosomal rearrangement (Carleson 2002). Along with comparing current chromosomal composition, scientists have been able to remodel the chromosomal configurations in sequence and in timing. This affirms the rearrangement rate in murid rodents is higher in the primate lineage than previously thought. The ancestral core of rats consists of approximately 40% of its euchromatic rat genome, which aligns with the genetic sequences of humans and mice (Carleson 2002). 95% of the ancestral core consists of known coding exons and noncoding regulatory regions. With a comprehension of the rate genome and the knowledge of its higher mutation rate, it yields genetic novelty and a better understanding of the mutation that could potentially be applied to the synthesization of medicine for current diseases present in humans.

Results

The conservation of sequences has aided in the identification of noncoding regulatory elements, which include locus-control regions and transcription-factor binding sites. The nucleotide element LINE-1 was present prior to the splitting of the orders primates and rodents, and it is still recognizable in rats (Walker 2009). 28% of the rat euchromatin aligns with the euchromatin of the mouse. 40% of euchromatin they share consists of

repeated elements that are present in only rodents. Such elements include B2 SINEs and the extinct B4 element. The remaining 72% of the rat's euchromatin includes rat/rodent-specific repeats that are no longer in the mouse genome. When searching the human genome for 109 transcription-factor binding sites, the number of potential sites reached over 186,000,000. With the conservation of the genomes of rats, mice, and human, the number of potential sites significantly decreased to 4,000,000 (Walker 2009). With such increase in specificity, the conserved sequences aided in the location of enhancer sequences and boundary elements. 40% of the rat and mouse genome constitutes immobilized transposable elements. The human genome consists of 50% of immobilized transposable elements (Walker 2009).

Discussion

The rationale behind the reason why rats are the primary research models is because of their large number of strains (728) (Carleson 2002) and a majority of them were developed as models for common diseases in humans (Shimoyama, RGD, personal communication). There are 708 QTLs (Quantitative Trait Loci) in rats that contain alleles for many present-day diseases.

Rats have approximately 2.75 billion base pairs in their genome, while humans have 2.9 billion base pairs. A majority of genes associated with diseases in humans have

counterparts in the rat genome, making the rat an excellent test subject for biomedical research (Zerhouni 2004).

Humans have 23 pairs of chromosomes while rats have 21, and there are approximately 280 large regions of similarity in the chromosomes of humans and rats. The threadlike structure of the nucleic acids contains information for composition in the form of genes. The sharing of some equal gene sequence results in similar cognition and responses in humans and rats (Bethesda 2004).

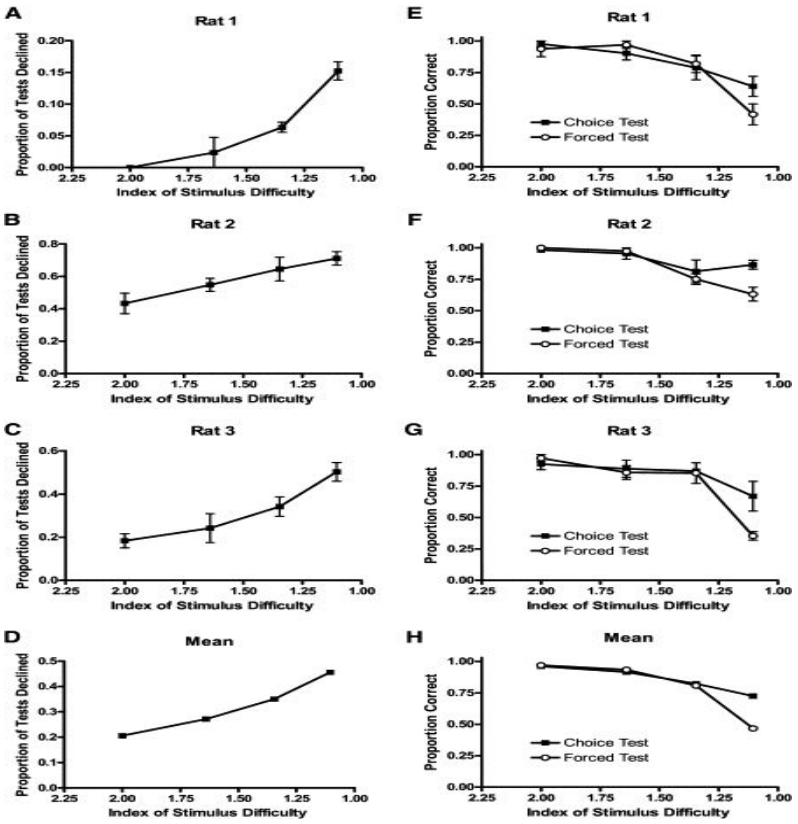
For the genus *Mus*, out of the 4,000 genes that were studied, only 10 genes were present in one species and not the other (human and mice) (Consortium 2000). Approximately 90% of the genetic makeup of mice consists of noncoding DNA, that has no apparent function. Thus making it difficult to cognize its genes by looking at individual sequences. Current computational programs are unable to identify many coding sequences, increasing the degree of difficulty of trying to identify regulatory regions within the DNA. The protein regions of the human genome are 85% identical to the mouse. The noncoding DNA has significantly less similar regions, around 50% (NHGI 2000).

Little is known about nonhuman primate laughter and humor. Neuroscientist Jaak Panksepp performed an experiment where he placed a brown rat in a caged environment and continuously tickled the rat. Tickling stimulated a 50-kilohertz

ultrasonic chirp from the rat. Rats are particularly ticklish in their nape area. After Panksepp stopped tickling the rat, the rat began to frolick and pursue the researcher's hand in order to be tickled (Panksepp Dr., 1990).This realization has prompted speculations of social-joy in rats. Human laughter involves a vocalized inhalation accompanied with pulsating sound bursts. Both rats and humans have distinctive forms of laughter, but their ability to laugh is an important communicative-affective component in their engagement in social roles (Bering 2012). The rats who emitted the most 50-kilohertz chirp were the most playful among other rat subjects (Panksepp Dr., 1990). A variety of aversive laboratory settings reduced laughter among the test subjects. The chirping decreased when rats were exposed to cat odor, when they were hungry, and when they were exposed to bright lights during tickling (Bering 2012). Rat's ability to laugh is dependent on its current state and external stimulus, which can also be said about human's ability to laugh.

Rats are able to perform metacognition, making them able to mentally synthesize thinking, classifying the rat as a naval gazer (Foote and Crystal 2007). A 2007 study at the University of Georgia, used food as a rational motive to stimulate thinking in rats. They were tried on familiar and unfamiliar information . Rats were trained to press a small lever when they heard a short burst of static and another lever for a long burst of static. If they pushed the right lever, they were awarded food pellets. They made it harder for the rats, and when the rats couldn't distinguish which lever to press they did

not perform the actions when they could distinguish the sound (Foote and Crystal 2007).



The results above represents graphed data from the experiment of performed by Allison Foote and Jonathan Crystal. The x-axis of the graph represents the difficulty of distinguishability of the stimulus, and the y-axis represents the correctness of the rat in pressing the correct lever. The results show a correlation between difficulty and correctness: as the difficulty increased, the degree of accuracy decreased. As the complexity of distinguishability of the sound increased, the rat began to not attempt to press a lever, accepting that they are unable to distinguish the sound (Foote and Crystal 2007).

Rodents exhibit a wide range of social systems. During comparative behavioral studies of rodents, the social roles of rats are split primarily into a solitary role and a social role (Armitage 1981; Blumstein and Armitage 1998). Adults in solitary taxa live alone with very little spatial overlap with conspecifics. These members live in discrete groups, within which there is extensive spatial overlap among adults- some group living is necessary because of some form of cooperation and conflict, which can also be said about humans (Hoogland 1995). This variation in social behavior, combined with the geographic distribution of individualistic and group living, provides an ecological explanation for group living in rats that have become known as the aridity–food distribution hypothesis. The aridity-food distribution hypothesis argues that the energetic cost of burrow excavation determines whether a species of mole-rat is social (Bennett and Faulkes 2000; Jarvis et al. 1994; Lacey and Sherman 1997). The more tenacious the rats are about finding food, the more likely that they will interact with other rats. Burrow excavation is also determined by soft soils, predictable periods of rain, and evenly distributed and moderately sized food resources, which may have altered the results.

Unlike humans, the sense of smell in rats, is the most important source of information about the social and nonsocial world (Sachs 1999). Different scents elicit different pheromones, which is defined by some scientists as anybody of odor that influence interactions between individuals of a species, even if the response is minute. Certain

odors from one individual can have strong effects on behavior, physiology (Brown and Macdonald 1985). While this is true, the response of humans to certain odors is much smaller than rats. An odor from female Norway rats (R. norvegicus) causes erections in males (Sachs 1999). Limitations in trying to understand specific rat responses to different types of odor is that relatively little is known about the particular chemical compounds that are responsible for the effects observed.

Rat experimentation is oftentimes under scrutiny for being unsafe, expensive, and unreliable. The structural differences, although they have many similarities, can result in inadequate information when trying to apply them to human diseases, despite some success. Drugs that have worked on rodents have not always worked on humans. About 95% of cancer drugs that enter human clinical testing fails (Klausner 2011).

Conclusion

Oftentimes mice and rat experiments are done as an attempt to discover and further understand the human genome, assuming that certain bodily processes in mice and rats are the same as humans, or at least similar enough to draw conclusions by analogy. But not all processes are analogous. Similarities in genetic makeup have allowed for many advancements in science fields. Scientific experiments with rats as the model have helped advance research in psychiatric disorders, cardiovascular diseases, diabetes, transplantation, wound/bone healing, neural regeneration, and space motion

sickness (Consortium 2000). While similarities are a big reason for rat testing, rats are also much easier to use in a controlled experiment due to their small size and their high reproduction rates. And now that the entire rat genome has been configured, scientists are able to manipulate the genes of rats to create exact replicas for proving/testing theories and/or hypothesis. With correspondence in genetic composition comes likeness in certain behaviors and social relationships among the same species. Limitations still are present as certain aspects of the genome in rats and humans are still unknown.

The rat currently remains as the ideal research model for experimentation because of their several similarities with the human genome. Various experiments have allowed use to understand socialization of rats, and how they are similar to humans, and to better understand the human genome. Many distinctions are apparent between the two species in phylogenetic structure and behavior, highlighting the 3. Rodent experimentation continues as the cure for diseases like cancer are continuing to be pursued, and its genome continues to be used to understand more gene sequences that are present in both rats and humans.

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