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Review

A Review of Animal Laboratory Practice in the COVID-19 and Safety Concerns

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HIGHLIGHTS

- Many research projects involving animal studies have faced interruptions due to the coronavirus disease-2019 (COVID-19) pandemic.
- The disruption in such research projects have raised significant concerns in biomedical scientific research worldwide.
- This study provides evidence on the feasibility of continuing the research activities in animal laboratories during the COVID-19 pandemic.

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ABSTRACT

The research in biomedical sciences is based on basic research on animals. As a consequence of the coronavirus disease-2019 (COVID-19) pandemic, many research projects involving animal studies have faced interruptions due to the raised concerns about the safety of working with animals The disruption in such research projects have raised significant concerns in biomedical scientific research worldwide. It seems necessary to assess and evaluate the safety and feasibility of conducting research projects on animal models. This study provides evidence on the feasibility of continuing the research activities in animal laboratories during the COVID-19 pandemic. According to the results of studies, the risk of COVID-19 is low in routine laboratory animals, including mice, rats, and pigs.

By examining the available data from our animal laboratory, continuing research activities on low-risk animals, with adequate safety and personal protection equipment being available at the facility, animal studies could be carried forward without endangering the safety of the researcher and the society.

Keywords: Coronavirus; Animal Laboratory; Biomedical Research; COVID-19

Introduction

Different animals have been used in medical research since the ancient Greek civilization (1). The discovery of biological and genetic similarities between human and animals has led to the development of the use of animal models in medicine and biological research (1), rendering the role of the animal laboratories in the development of biological sciences indispensable. With the emergence of the global pandemic of coronavirus disease-2019 (COVID-19) around the world, veterinary societies became concerned about the possibility of contamination of laboratory animals with COVID-19 and the possibility

of cross-species transmission to humans. Therefore, most laboratories and animal studies have been closed or restricted their activities by reducing the presence of staff to reduce any possible contamination (2). All biomedical sciences depend heavily on animal experiments therefore such a global halt in all animal study and research projects during the COVID-19 pandemic could lead to a disruption in the evolution of knowledge and science with grave consequences on clinical and daily life use. Many questions are still being asked globally from experts regarding whether it is ethical and feasible to continue the current projects or start new ones. Also, given the cost and time spent on each project, the cost-effectiveness of such research might remain questionable to the extent that the complete shutdown of animal laboratories and projects are being assessed as an option by some authorities around the world.

Evidence acquisition

Almost 75% of human infectious diseases are transmitted from animals (3). Genetic sequencing analysis has shown that COVID-19 is closely related to other viruses in the coronavirus family that circulate in bats (4). Also, in some reports bats have been identified as the natural source of the emergence of COVID-19 (5). These reports raised concerns about the transmission of the virus from animals to humans. But so far, there is not enough scientific evidence for the origin of the virus and how it is transmitted to humans (6). On the other hand, the first person with COVID-19 in Wuhan, China, had no connection with the bat or the seafood market (7). It should also be noted that there is very little evidence of animals being infected with COVID-19 (some domestic cats, dogs, minks, and a tiger), and infection in these animals, is likely to be transmitted from infected owners or other peoples (8). Also, there is no evidence that the disease is spread by animals around the world (6).

The severity of COVID-19 in animals is also low, and COVID-19 generally presents without symptoms or some mild clinical symptoms. One of the infected animals was an asymptomatic dog belonging to a COVID-19 patient in Hong Kong (9). COVID-19 infection in this dog was confirmed by reverse transcription polymerase chain reaction (RT-PCR), and serological tests revealed the presence of COVID-19 specific antibodies (10). However, due to the low viral titers observed, the virus did not grow and remain weak in this dog, and the chance of infectious transmission was very low or nonexistent (10). Therefore, COVID-19 could sometimes infect an animal which might not lead to clinical illness in that animal, nor becomes transmissible to others animals and people. Another infected dog in Hong Kong was a German shepherd belonging to a person infected with the COVID-19 (11). The dog had no clinical symptoms, while the polymerase chain reaction (PCR) test was positive. Viral sequencing of this dog and its owner showed that both viruses were identical and the dog was infected by its owner. Like the previous animal, in this case, the viral load was very low and there was no possibility of transmission from this dog (12). Other infected animals were a cat in Hong Kong and a cat in Bruxelles (13). Despite the positive PCR test in these two cats, no evidence of disease transmission to other human or animals were found. Also, on April 5, a positive molecular test for COVID-19 was reported on a tiger at the Wildlife Conservation Society's Bronx Zoo with a clinical sign of a dry cough. Zoo officials believe the tiger may have been infected by its guard (14). However, it should be noted that positive reverse transcription–PCR (RT-PCR) results do not confirm the presence of the living, replicating virus, and it does not necessarily mean the subject is contagious (8). Finally, there is no definitive evidence that animals play a role in the distribution of COVID-19 (4).

Risk of COVID-19 infection in different animals

Because of the genetic differences between laboratory animals, the risk of developing COVID-19 in each species is different (20). Preliminary studies investigating the susceptibility of commonly used animals to COVID-19 have shown that cats are the most susceptible animal to be infected by COVID-19 in the laboratory and the virus can cause clinical disease in them (6). In the second place, ferrets are susceptible to the virus, but are less likely to develop a disease compared to cats (6). Dogs are also likely to be susceptible to the virus but are much less likely to present clinical disease (6). In the laboratory, fruit bats were also infected with the COVID-19, but their infection did not lead to clinical disease and most probably they are not contagious (6). Monkeys are also susceptible to COVID-19 and infection occurs in them with mild symptoms (15). Meanwhile, these studies have shown that poultry and pigs are resistant to COVID-19 infection (6). In biomedical studies, mice and rats are the most widely used animals (16) and their susceptibility worth being examined. The COVID-19 virus uses angiotensin-converting enzyme 2 (ACE2) protein to enter its host cell (17). Examination of the ACE2 receptor for the entry of the COVID-19 virus into the cells showed that the mouse and rat ACE2 were unable to transmit the virus into the cells (18, 19). Hence, in COVID-19 vaccine studies transgenic mice and rats that express human ACE2 are being used (19). According to the abovementioned reports, there are far fewer safety concerns about working with mice, rats, poultry, and pigs (all with wild type ACE2 receptor gene) in animal laboratories during the COVID-19 pandemic.

The susceptibility of different mammalian species (rhesus, macaque, marmoset, hamster, rabbit, ferret, rat, mouse, pig, and bat) to the COVID-19 has also been

evaluated *in silico*. Hence, 29 important ACE2 amino acids responsible for the entry of the COVID-19 into the host cell in some species were compared with the human ACE2. The results of the alignment analysis of this protein showed that rhesus macaque ACE2 was 100% similar to humans, followed by marmosets (90%), hamsters (86%), rabbits (83%), pigs (76%), bats (69%), mouse (62%), ferrets (59%) and rats (55%) (18). Therefore, according to *in silico* assessment, the rhesus macaque, marmosets, and hamsters are the most sensitive species.

Our experience in the time of COVID-19 pandemic

At the time of the outbreak of COVID-19 in our animal laboratory of the Urology Research Center of Tehran University of Medical Sciences, eight animal projects (84 rats) were in progress. During the first wave of the pandemic, these projects were carried on by regulating and reducing the presence of laboratory staff and ensuring the health of those entering the laboratory. Any employee who developed symptoms of (fever, cough, muscle pain, throat pain) was removed from the working list and was denied access to the facility for 14 days. Also, physical spacing was increased between the animals. No clinical infections and COVID-19 viruses were detected among our staff nor studied rats, and all eight projects were completed according to the respective protocols (Figure 1). Of course, we noted that in quarantine conditions, the provision of materials and equipment is slower and more difficult than other times. Therefore, with proper storage as well as the necessary coordination regarding out-of-laboratory equipment (such as computerized tomography (CT) scan device and pathology equipment), we did not encounter any problems in carrying out protocols without serious deviations. In projects that required the removal of rat organs for autopsy, the organ was collected and pathological examinations were performed in full compliance with the required biosafety principles. At the end of the project, all the animals were euthanized and discarded according to local biosafety protocols.

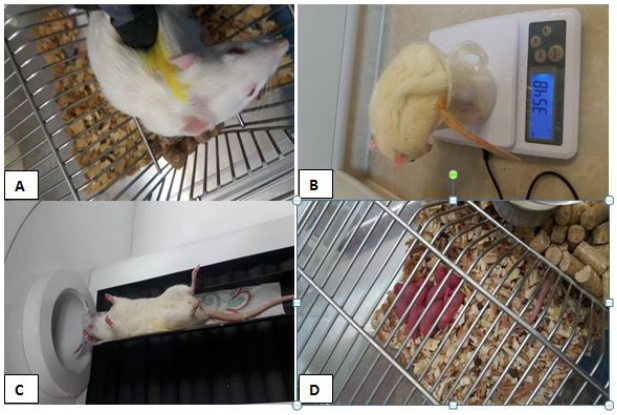

Figure 1. Activity of the Animal Laboratory of the Urology Research Center of Tehran University of Medical Sciences during the COVID-19 pandemic. A) Creating social distance between animals. B) Check the health of animals during projects. C) Provide the necessary equipment (for example, CT scan) to continue any project. D) Keeping animals with children on separate shelves.
CT: Computerized Tomography

Conclusions

During the pandemic of COVID-19, animal laboratories need to adapt to the special conditions which are far beyond simple biosafety precautions, in order to be able to complete their ongoing projects. It could be very useful to be aware of the sensitivity of the selected animal to the COVID-19 infection. Also, re-evaluation of the supply chain for materials and equipment during quarantine is of utmost importance for the successful execution of research protocols. Daily health checks of laboratory staff and daily monitoring of animals' clinical symptoms are essential. Finally, laboratory staff needs to have complete personal protective equipment.

Authors' contributions

All authors had an equal contribution.

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Conflict of interest

All authors declare that there is not any kind of conflict of interest.

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Ethical statement

Not applicable.

Data availability

Not applicable.

Abbreviations

ACE2	Angiotensin-converting enzyme 2
CT	Computerized tomography
PCR	Polymerase chain reaction
RT-PCR	Reverse transcription–PCR

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