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Editorial

The Sheep as a Large Animal Experimental Model in Respiratory Diseases Research

La oveja como modelo experimental de animal grande en la investigación de patologías respiratorias

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The use of animal models obtained through genetic manipulation has proven to be very useful for identifying the physical and pathological mechanisms in many different diseases.[1,2] However, some publications have pointed out the lack of agreement between experiments performed in animal models and clinical trials in humans.[3] These divergences have been associated with both the unnatural acquisition of the disease in experimental settings and the major anatomical, genetic, dietetic, environmental, toxic, and immune differences between animals and humans.[4] In addition to these differences, a significant percentage of the experimental methodologies used in publications are deficient in quality. As such, several authors defend the need for an urgent restructuring of these experiments, including improved methodology in clinical trials with the same rigorousness as those performed with human subjects (adequate number, randomised sample, double blind setup, methods for results analysis, etc.), a record of trials and procedural protocols for systematic reviews and meta-analyses, and improved communication between those groups dedicated to animal experimentation and those who work with humans in the clinical setting.[3-5] This would all serve to improve the application of results obtained from animal studies in humans.

This situation has led to the need, at least in clinical trials with drugs or other types of treatment, for animals that offer clear advantages as model systems, whether because they naturally share diseases with humans or have a development similar to that suffered by humans. Although murine models offer research advantages in some respiratory diseases due to their manageability, cost-effectiveness and versatility,[2,6] different research groups in recent years have singled out their limitations for evaluating the response to treatment in different diseases.[7,8] Animals such as dogs or sheep have been proposed as useful animal models, and although certain barriers exist to using them, above all economic barriers, there is a strong current of opinion that is promoting their use in circumstances in which the advantages surpass the inconveniences.

In the case of sheep, Australian researchers have highlighted the potential for their use in biomedical research, above all for respiratory diseases.[9] The anatomy and physiology of the sheep respiratory system is more similar to that of humans than rodents, and has been proposed as a good model for vaccines, asthma pathogenesis and inhalation treatments. Furthermore, it is a large animal (30-90 kg, according to sex and race) with well-studied anatomy and physiology, is easy to cannulate, and provides ease in taking frequent and/or large samples. Also, it provides a very useful specimen for surgical trials, measuring certain respiratory parameters and many other processes which cannot be carried in rodent models. All these advantages would make the sheep an optimal study animal, especially in research on respiratory diseases.

Starting with an important pathology such as asthma, and in light of the lack of a universally accepted animal model for this problem,[6] sheep are placed along with dogs as the model for particle-induced diseases and the development of allergies with certain advantages over rodents, especially in studies on the inflammation of the lower respiratory tract.[9,10] A sheep model naturally sensitised to the nematode *Ascaris suum* has been used for over a decade in research on involved basic mechanisms and in the study of new drugs.[11] Furthermore, researchers have long been searching for an "asthmatic" animal model that could be triggered by an aeroallergen also capable of causing the disease in humans, and recently, Australian authors have developed an ovine model for asthma induced by dermatophagoides.[12]

Continuing with other respiratory diseases, the ovine model has been used for physiopathological studies of acute bronchial obstruction and adult respiratory distress syndrome provoked by massive inhalation of smoke and hot air.[13] It has also provided a

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model for infant respiratory distress syndrome (IRDS) using premature lambs, and has facilitated research into the regulation of surfactant proteins.[14] The findings have led to the development of new treatments such as nebulised surfactant, vasodilators, mechanical ventilation systems and extracorporeal membrane oxygenation.[15-17]

Meanwhile, sheep are also susceptible to natural bacterial infections shared with humans. Recent publications on pneumonia and sepsis associated with methicillin-resistant *Pseudomonas* and *Staphylococcus* in sheep[18,19] could facilitate a study of colonisation of the airway and ventilator-associated pneumonia caused by these microbes.

Sheep have also been proposed as an animal model for lung cancer research. The clinical and anatomopathological similarities between a natural sheep lung tumour, known as an Ovine Pulmonary Adenocarcinoma (OPA), and human bronchioloalveolar carcinomas have been highlighted on several occasions.[20] OPA is caused by a beta-type retrovirus known as jaagsiekte sheep retrovirus (JSRV). No known human lung cancers are associated with a retrovirus, although some studies suggest the participation of a retrovirus in some types of bronchopulmonary cancers.[21,22] In addition to this, OPA could serve as a model for lung cancer with other applications that are difficult to develop in small laboratory animals. JSRV can be cultivated in the laboratory in large quantities and inoculation of this virus in lambs reproduces the lung tumour quite rapidly.[23] Although the model requires the use of a complex infrastructure,[24] it allows for monitoring the course of the tumour by radiological and endoscopic methods, as well as treatment trials that can be better evaluated in large animals, such as radiofrequency ablation and inhaled anti-tumor treatments. This ovine lung cancer model provides an additional advantage. Several studies indicate that a viral surface protein is involved in the JSRV-induced transformation of type II alveolar cells and Clara cells, acting as an oncoprotein and stimulating MAPK (Mitogen Activated Protein Kinases) and PI3K/AkT (Protein Kinase B) signalling pathways.[25,26] These pathways are active in many types of cancer, such as lung adenocarcinomas.[21] Therefore, this animal model could serve for studying the effects of anti-tumor drugs that act by inhibiting some of the MAPK and PI3K/Akt pathway elements.[27]

Although these diseases have created the greatest amount of interest in this field in recent years, the ovine model has traditionally been used for studying the mechanisms implicated in the regulation of the respiratory and cardiovascular systems. However, the description of these findings exceeds the limits of this editorial.

We will finalise our editorial by emphasising our adherence to an old idea that has been brought up in recent years. We refer to the "One Medicine" concept, which is based on the convergence of human and veterinarian medicine. This movement, which human medicine gave birth to at the end of the XIX century, was reborn during the last century by the veterinarian Calvin Schabe and has been taking on steam in recent years. It promotes the reunification of the medical and veterinarian professions with collaborations in all fields of medicine.[28] In recent decades, new diseases acquired through contact with other species have appeared, such as HIV, ovine spongiform encephalopathy, and, in the case of respiratory diseases, SARS-type infections and the A H1N1 flu, which require collaborations between human and veterinarian medicine. Attesting to this renewed interest, health authorities and professionals from countries such as the United Kingdom and Canada have designated research funds towards multidisciplinary groups including doctors and veterinarians in the study and management of these diseases.[29]

As we have indicated, human and animal health sciences have important connections and aspects in common that strongly justify a more unified collaboration between the two fields. These collaborations already offer important results such as those briefly mentioned in this editorial, where the veterinarian knowledge on sheep physiology, anatomy and diseases offers major advantages for research on medical respiratory problems. If policies were generally established in which research plans that tended towards integrated projects on human and animal medicine were also present in Spain, we would probably be able to better take advantage of the economic and human resources available to us and, more importantly, the possibilities of solving our problems would multiply.[30]

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