

MINIATURE PIG IN FRANCE: OUTLOOK AND CHALLENGES

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ABSTRACT

The INRA (French National Institute of Agronomical Research) is a French public research institute. Its experience in animal production is recognized and the institute is also involved in human nutrition research. In Europe, a decreasing use of primates in research is planned. Consequently, increasing needs for alternative solutions are expected. The Göttingen miniature pigs, which is the only breed available and well referred in Europe, does not completely fulfill the expectations and needs of INRA researchers. In this context, it was a logical choice for the INRA to create its own miniature swine breeding facilities, with the aim of sharing this tool with the whole French research community. Three breeds have been purchased to compose the breeding stock: Vietnamese potbellied miniature pig, Pitman-Moore and Yucatan. This presentation deals with the INRA's miniature pig project. The institute has initiated this program aimed at characterizing the miniature pigs for human nutrition research. In parallel, we are gathering bibliographic references, available knowledge and advices on miniature pigs to build and share our expertise with the laboratories that are interested in this animal model, and notably with groups that have never used this model and would like to benefit from its multiple advantages. Ethical aspects in conjunction with specific scientific purposes must also be considered for the improvement of handling, surgery and husbandry techniques, in order to provide the best recommendations possible to make the minipig model a real asset in addition to more conventional animal models.

Key words: Biomedical research, Human nutrition, Miniature swine, Pitman-Moore, Vietnamese potbellied miniature pig, Yucatan

INTRODUCTION

Since a long time, animal models are used in biomedical research to investigate human diseases, improve their diagnostic, study their etiology and develop new therapies. For these purposes, non-human primates are considered as good models. Nevertheless, they are expensive, difficult to handle and need substantial investments in facilities and technical workers. Rodents have the advantage to be cheaper and easier to breed, but they are also further from humans in terms of phylogeny. On the contrary, the pig shares many features with the human, in terms of anatomy, metabolism, physiology and behavior, in addition to have an omnivorous diet like the human (Azria and Kiger, 1972 ; Hitz *et al.*, 1987 ; Vodicka *et al.*, 2005). The pig is consequently a good model, and particularly for human nutrition (Weaver and Mc Kean, 1965). Because of its size and rapid growth rate, conventional pigs are

not the best models. Miniature pigs are a good compromise when considering size and growth rate, and they are easier to handle and cheaper to breed (Bustad and Mc Clellan, 1966).

INRA is involved in human nutrition research and several teams are more specifically interested in diabetes and obesity. On these topics, long-term experiments are often mandatory to study the life-long consequences of different nutritional environments. Consequently, the use of miniature pigs instead of larger production pigs makes sense. There are a lot of published references available on miniature pigs, but data were generally obtained under different experimental conditions and at different physiological stage, with different criteria recorded and on different breeds. To our knowledge, In Europe, the Göttingen miniature pig is the only miniature swine breed commercially available and well referred for research. The problem is that animals are sold by a private company with a restrictive use policy. Others facilities exist like melanoblastoma-bearing Libechov minipig in INRA Jouy-en-Josas or the Munich miniature swine (also a melanoblastoma-bearing strain) in Munich University but dedicated to strains selected on specific purposes and not necessarily suitable for others. In this context, the INRA decided to produce miniature pigs on its own in order to control the breeding environment and conditions (mating, genetic, feed, etc.), to fulfill the scientists' specific needs, and ultimately to create a new breed of miniature swine that would be particularly adapted to human nutrition research. This presentation deals with the INRA's miniature pig program, its outlooks and challenges.

DISCUSSION

Outlooks

The use of non-human primates for research in Europe is regularly brought into question by animal protection lobbies and will be affected by new ethics regulations in the near future. Primates used in research will have to come from breeding facilities where no animal has been removed from its natural habitat. In addition, their use will be limited to well-defined health purposes, such as serious infection or neurodegenerative diseases, and only when replacement by other models is not possible. The rodent models have their specific advantages and remain unavoidable in many instances, but the need for substitution models is present, in France, Europe but also worldwide, and the miniature pig appears to be a good alternative (or complementary approach) to more conventional models.

Most of the miniature swine breeds developed for research were selected mainly on body size (especially because of crossing with larger commercial pigs) and not necessarily on the basis of scientific criteria (Panepinto, 1996). Such selection on size was based on weight at early stage with the risk to select "runts" and not the smaller matured animal (Panepinto and Phillips, 1981). Nowadays, size is still one of the major selection criteria and arguments of the private companies to sell miniature pigs. When the INRA decided to launch the "minipig program", the initial strategy was to buy breeding stocks from existing breeds originally miniature to avoid the aforementioned selection problems. Three breeds were found available for purchase for breeding purposes: Vietnamese potbellied miniature pig, Pitman-Moore and Yucatan. After a preliminary study focused on eating behavior, the first breed has been rejected because the results obtained were not conclusive. A set of studies aimed at investigating the behavioral reactivity and social aptitudes of Vietnamese, Pitman-Moore and Yucatan minipigs have been conducted in parallel, and the results are being published (Val-Laillet *et al.* 2013, Val-Laillet *et al.* in preparation, Meunier-Salaün *et al.* in preparation), highlighting significant differences between breeds. According to previous

knowledge (Panepinto *et al.*, 1985) and observations performed in our breeding facilities, the Yucatan breed appeared of particular interest for the “minipig project” on human nutrition. Consequently, we chose to increase the number of Yucatan miniature pigs in order to better characterize this breed as a first step. Detailed characterization of the other breeds will follow in due time, and crossbreeding might be considered if relevant and necessary.

Challenges

The main interest of the INRA is to provide a relevant model for human nutrition. The minipig program is still in the beginning stages and the first step will be to comprehensively characterize the actual breeding stock. If all traits of interest (in terms of physiology, behavior, propensity to declare obesity, etc.) are identified in the actual stock, the aim will be to preserve a stable breed and its genetic pool. If some traits are to be modified or introduced, it will be necessary to initiate crossbreeding of the three available breeds, or to find new miniature pig populations or breeds expressing these traits. This eventuality probably means purchasing animals from foreign country, with all the legal and administrative difficulties that such a procedure implies.

Another challenge is to adapt (and/or position) our miniature pig model to well-defined scientific questions and purposes, which is a *sine qua non* condition to be able to provide counseling and services to a wide scientific community. When relevant and necessary, our objective is also to provide an access to our facilities to perform experiments in collaboration with our scientists. When confronted to the necessity to develop or use a new animal model, scientists have to face many kinds of potential problems: 1) the fear of changing one’s model, taking into account individual preferences and past works, and especially the uncertainty about what this new model will permit in comparison with the other models; 2) difficulties to adapt facilities, supplies and management procedures to the new model; 3) having trained technical workers to handle this new model in adapted husbandry. For example, we recently supplied some miniature pigs to a laboratory of which the scientists were used to work with non-human primates only. Counseling on housing, feeding and sanitary questions, as well as practical help in terms of husbandry or surgery matters, was really helpful to the scientists and technicians. Knowing that they could rely on our experience was a good reason (and even guarantee) to use this model for the first time.

An additional challenge is to improve our methods and to provide innovation in terms of animal handling, surveillance and care. Technical progresses like telemetry, pain consideration and treatment, and post-surgery surveillance will improve both our experimental procedures and quality of scientific results. For instance, pigs and miniature pigs are used for training courses in human surgery, and for the development of new techniques or skills, especially less invasive procedures. Adapting human surgery strategies, such as coelioscopy, to miniature pigs leads to the improvement of animal welfare as well as of scientific results since the animals need shorter recovery periods and less analgesia or antibiotics. Amongst the future techniques that might be used to increase breeding possibilities are artificial insemination and embryo transfer. Artificial insemination is well mastered in pig production, but embryo transfer methodology needs some developments before being currently applied to minipigs. On this topic, one laboratory in France contacted us to work on transplant and gene transfer.

CONCLUSION

At the present time, a great proportion of the international research using minipigs is focused on toxicology and drug market authorization. The INRA is attached to develop a model specific to human nutrition, but there are a lot of other potential applications for minipig models. Studies focused on cognition and brain disorders for example often use non-human primates, but if the use of these models becomes more and more difficult to justify, the minipig has a high potential for this kind of research (Lind *et al.* 2007). Specific minipig breeds could be created for specific scientific purposes (e.g. a French institute is interested in selecting animals for organ transplant, to work on cancer therapies) and knockout models could even be proposed for various applications (e.g. Cao *et al.* 2013, Diswall *et al.* 2008).

Another surprising market opportunity for miniature pigs is their use as companion animals and in zoo exhibits. In USA, several children's zoos and petting zoos have made the choice to buy miniature pigs. In France, a zoo was interested in purchasing Yucatan miniature swine. If this market is still confidential, it exists and might be considered too in the future. We already interacted with a few labs, which contacted us by themselves. These experiences let suppose that more labs are interested in and collaborations will probably increase in number. But, for the moment, we are focused on the minipig program. We continuously need to improve our knowledge in every aspect of minipig breeding, to fulfill the scientists' specific expectations and provide the best breeding conditions and practices, with respect to ethical standards and societal responsibilities.

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