Animal Source

PSU Animal Resource Program

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Inside this issue:

Do You Hear What I Hear? Vocalization and Hearing in Mice

Mice are capable of producing both audible and ultrasonic vocalizations in the larynx by passing air over the vocal cords. Audible vocalizations such as squeals and squeaks are made by vibrating vocal cords. Ultrasonic vocalizations are created when the vocal cords are constricted so tightly that they no longer move. In this case, the constricted vocal cords function in a manner similar to a whistle. Both male and female mice produce both types of vocalizations during various social interactions.

Audible vocalizations are emitted by adult mice primarily in response to or anticipation of a painful stimulus. They can be heard during agonistic encounters between mice or sometimes when handled by humans. Investigators have theorized that the squealing may serve to inhibit agonistic or sexual behavior.

Ultrasonic vocalizations in adult mice are emitted primarily by males during courtship and mating. It has been suggested that these vocalizations signal to female mice that the male is sexually motivated, possibly reducing female aggression. Some authors have even demonstrated that mice produce complex ultrasonic phrases that may be analogous to bird song. Ultrasonic vocalizations are not essential for reproductive success, however, as deaf mice can mate without difficulty.

Although mice are capable of producing sounds that function in communication, the relative importance of vocalization to mouse social life has not been determined. Several inbred mouse strains have been shown to suffer from progressive hearing loss but appear to be capable of normal survival and reproduction in the laboratory.

Inherited hearing loss in these strains is due to progressive degenerative changes in cochlear tissue. These changes typically start in the area of the cochlea that is responsible for high frequency hearing. For example, C57BL/6J and BALB/c mice hear normally when young but develop significant high frequency hearing loss by 6-12 months of age. DBA/2J mice likely never hear high frequencies (>25 kHz) well and develop severe loss of sensitivity to both high and low frequencies at 1-2 months of age.

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New Drug Development and the Use of Animals

The FDA estimates that it takes approximately 8 ½ years to study and test a new drug before it can be approved for the general public. This estimate includes early laboratory screening and animal testing, as well as later clinical trials using human subjects. Drugs may be developed to treat a specific disease or discovered by accident. An example is Retrovir (zidovudine, also known as AZT) which was first studied as an anti-cancer drug in the 1960's. Although zidovudine failed as an anticancer drug, it was rediscovered as an AIDS treatment in the 1980's and approved for that purpose by the FDA in 1987.

Initially, pharmaceutical companies screen many chemical compounds in test tube experiments and computer simulations to find one that shows promise as a new drug. Before it can be tested in humans the company must submit data to the FDA showing that the promising compound is reasonably safe. To accomplish this, the company must complete preclinical studies in animals to develop a pharmacological profile of the drug, determine the acute toxicity of the drug in at least two species of animals and conduct short-term toxicity studies ranging from 2 weeks to 3 months. Long-term (2 year) carcinogenicity studies in animals may continue after human clinical trials have begun.

Most drugs that undergo preclinical testing never make it to human testing and review by the FDA. Those that do must then undergo extensive clinical trials in humans which can take several years to complete. It has been estimated that for every drug that is eventually marketed to the public, the pharmaceutical industry invests $2 billion dollars.

More information on new drug development and the FDA approval process may be found at http://www.fda.gov/cder/regulatory/default.htm.

Swine as a Model for Diabetes Research

It has been estimated that 7% of the U.S. population suffers from some form of diabetes. Diabetes includes multiple diseases characterized by high blood glucose levels and defective insulin production or action. Millions of dollars are spent every year on research into the causes, treatment and prevention of diabetes. Animal models are an important tool in this research. Due to their anatomical and physiological similarities to humans the pig has become a common model in diabetes research.

Pigs produce insulin that is similar in structure to human insulin. In fact, Ebihara et. al reported that the pharmacological actions and pharmacokinetics between porcine and human insulin were nearly the same. Similarly, pigs can be bred to have very lean body composition or can be raised to have a high percent body fat to help study diabetes and obesity, and they have a relatively rapid growth rate which can be important in studying juvenile diabetes.

Two primary methods are used to induce diabetes in swine. Chemical destruction of pancreatic islet cells may be produced by giving one of two drugs, alloxan or streptozotocin, intravenously to a pig. Without functioning islet cells the pig can not produce insulin and will develop diabetes. Diabetes due to a lack of insulin may also be created by surgically removing the pancreas.

Regardless of the induction method used, the pig will require medical treatment to control the diabetes and allow survival for the duration of the experiment. Regulation can be challenging in this species and requires insulin replacement therapy, diet control and blood and urine glucose monitoring on a daily basis.

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Hematology and Blood Chemistry Services for Investigators

The Animal Resource Program (ARP) provides hematology and blood chemistry testing services to the research, extension, and teaching communities at Penn State. Available tests include complete blood count (CBC) and various blood chemistry tests, including liver and kidney function testing and T4 (thyroid) testing. Blood gas and electrolyte panels may also be run. Blood from several animal species, including rodents, non-human primates, rabbits, sheep, cattle, horses, swine, and deer may be analyzed.

Submission forms can be picked up at the ARP office or mailed to you through campus mail. Samples and submission forms may be dropped off during regular business hours. Results will be returned via email by the next business day. Call 865-1495 for additional information.

The next Mouse Biomethodology Seminar will be held on June 1, 2007 from 1-4 pm in the Centralized Biological Laboratory. Please call 865-1495 to register to attend.

Swine as a Model, continued from page 2.

Although they do not develop extremely high blood and urine glucose levels, unregulated diabetic pigs die within 10 days. Investigators must be aware of this and other complications that can occur when planning to use a diabetic pig model.

Swine are an important model in diabetes research and work is under way to further refine and develop the ways in which pigs may be used. Swine have been used extensively in cardiovascular research and it has been determined that diabetic swine develop more severe coronary atherosclerosis than nondiabetic controls. Atherosclerosis is the most common cause of death in humans with type 2 diabetes and the pig could be an ideal model for study of this aspect of the disease.

Further information on the use of pigs in diabetes research may be obtained from the references listed below or by contacting an ARP veterinarian.

Bellinger DA, Merricks EP, Nichols, TC (2006). Swine Models of Type 2 Diabetes Mellitus: Insulin Resistance, Glucose Tolerance, and Cardiovascular Complications. *ILAR Journal* **47**(3): 243-258.

Centers for Disease Control Diabetes Program: Data and Trends (5/4/2007). Online at http://www.cdc.gov/diabetes/statistics/index.htm

Swindle, M (1998). Surgery, Anesthesia, & Experimental Techniques in Swine. p120-121. Iowa State University Press.

Ebihara, A., K. Kondo, K. Ohashi, K. Kosaka, T. Kuzuya, A. Matsuda (1983). Comparative clinical pharmacology of human insulin (Novo) and porcine insulin in normal subjects. *Diabetes Care. Suppl.* Mar-Apr: 17-22.

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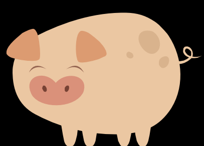

More than 54,000 pigs are used each year in biomedical research in the US. (USDA, 2004)

The Animal Resource Program (ARP) is committed to providing PSU research personnel with high quality animal care services and facilities, to facilitate and improve animal research, and to ensure the health, well-being and humane treatment of all animals at PSU. ARP provides veterinary and diagnostic services, personnel training and expertise in laboratory animal, agricultural and wildlife technology and medicine. ARP veterinarians have specialized training and are available to assist with animal model development, experimental design, budget projections and grant preparation. Participation in collaborative research projects is welcomed.

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In addition, many mutant mouse strains have been reported to suffer from hearing impairment or deafness. This type of deafness is commonly associated with balance disorders and pigmentation anomalies such as “shaker-waltzer” and “steel” types of mutants. Investigators should be aware that hearing impairment in certain strains and mutants can confound behavioral testing results. Poor response to auditory stimuli should not be attributed to a learning deficit in these mice.

The most widely used methodology to assess hearing in mice is the Auditory Brainstem-evoked Response (ABR). In this test, an electrophysiological response by the inner ear and auditory brainstem is evoked by a series of rapidly repeated tone bursts or clicks. These responses are recorded by electrodes attached to the animal’s scalp. Tone intensities are reduced in a stepwise manner to determine a threshold for detection of ABR’s. This threshold corresponds to the behavioral threshold for hearing. Normal mice have good sensitivity to tones from around 2 – 80 kHz. Abnormally high ABR thresholds suggest hearing loss.

References:
Holy TE, Guo Z (2005) Ultrasonic Songs of Male Mice. PLoS Biol 3(12): e386 doi:10.1371/journal.pbio.0030386
Willott JF (2007). “Factors Affecting Hearing in Mice, Rats and Other Laboratory Animals.” Journal of the American Association for Laboratory Science **46** (1): 23-27.
Willot JF, Ed. (2001). Handbook of Mouse Auditory Research: From Behavior to Molecular Biology. CRC Press: Boca Raton.