Radiotelemetry comes of age—perhaps just in time

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IN ACTUALITY, THE DISCIPLINE of functional genomics deals with the science and art of phenotyping. Identifying the genetic bases for complex integrated systems, as well as complex diseases, relies on the validity and accuracy of the “trait measurement.” Any trait, real or erroneous, may be mapped, whether in humans or animal models. Such errors in quantitative trait locus mapping, or even gene assignment, may be compounded because few replicate studies are conducted. In an effort to avoid such errors, behavioral scientists use three tests of “validity” for a trait (phenotype): “construct,” “face,” and “predictive” (11, 12). However, even these tests may be insufficient if the actual measurement methodology is compromised. There may be many reasons that contribute to inadequate, inappropriate, or erroneous phenotyping, among them the potential interaction between the experimenter (or environment) and the test subject. In human studies the cognitive capabilities of the test subject present the challenge. This problem is further exacerbated with animal models, mainly due to the inability to bridge the cognitive gap between animals and humans. One cannot simply ask a rat or mouse how they feel that day or whether the technician’s aftershave lotion is disturbing to them!

Technology has encouraged major advances over the past decade in monitoring physiological and behavioral traits of human and model organisms. Among the factors contributing to these advances are innovations in the fields of computer and information technology, as well as miniaturization of instrumentation needed for telemetry or non-hard-wired monitoring. These advances address a major confound, the “biological uncertainty principle,” which derives from the influence of measurement method and/or experimenter on trait expression or subject performance. The development of small implantable telemetry probes has sparked a revolution in the laboratory not unlike that ignited in molecular biology and medicine through the discovery of thermostable polymerases and the development of the polymerase chain reaction. Commercialization of small implantable telemetry probes has made such instrumentation available to nearly every investigator. Recent advances in radiotelemetry probes provide new opportunities for real-time monitoring of traits such as deep body temperature; motor, neuronal, and cardiovascular activities; and even sleep states. Furthermore, radiotelemetry introduces additional opportunities in experimental design by permitting time-series measurements over days, weeks, and months. Transference of the methodology to even smaller rodents, such as Mus, combined with the assumption of the Mus species as an in vivo test tube, has resulted in the widespread use of telemetry techniques for trait quantification by laboratories that specialize in molecular and biochemical approaches. Unfortunately, during this same period of time there has been a decline in training scientists in traditional complex trait measurement techniques, notably in physiology and pharmacology. Yet the use of telemetry measurements to quantify and track complex traits with direct application to the field of functional genomics requires an understanding of the potential for such experimental errors. Here then is one conundrum.

Over the years, there have been several publications detailing validity testing of various telemetry systems; however, until recently (2000), few validation studies addressed the most widely used commercial unit. Instead, individual laboratories (3, 5), including my own (1), developed internal validation methods and/or relied on proprietary information from the manufacturer (Data Sciences International). In 2000 and 2001, three papers (2, 8, 10) appeared addressing surgical procedures and correct use of the system in mice. As a result of increased use of the commercial systems, additional reports appeared in 2003 seeking to validate procedures and instrumentation for various trait measurements including electroencephalogram and electrocardiogram (4, 6, 9).

The article by Leon et al. (7) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology addresses issues requiring validation of surgically implanted radiotelemetry probes and provides experimental details critical to the planning of experiments using telemetry. The authors compare and contrast the two rodent species widely used in physiological, toxicological, behavioral, and genomic studies, and select three stress-sensitive traits: body growth, circadian rhythmicity of core body temperature, and general motor activity. Two fundamental questions are asked in the study: how does surgical implantation affect growth rate and what is the effect of the transmitter mass and weight on trait expression in the two species? The Leon et al. study also examines the separate effects of anesthesia and laparotomy on trait expression. The experimental design, methods, procedures, and conclusions of the study are necessary reading for all biological scientists and students planning or currently employing radiotelemetry in small model organisms.

The study’s findings regarding postsurgery body weight changes are similar to those observed by many laboratories, including ours; namely, that after probe implantation, a model organism can take up to 14 days to achieve presurgical body weight levels. This is one reason why many laboratories commence telemetry monitoring 7 days after surgery, but wait 14 days before acquiring study data for analysis. Interestingly, the authors found that whereas food intake recovers rapidly after surgery, water intake parallels body weight and does not fully recover even by 14 days. Effects on circadian rhythm appear to be more transient, but are markedly species dependent. Regarding the issue of transmitter weight/size as a significant fraction of body weight, they conclude that the ratio of body weight to transmitter weight, as well as both the mode of attachment within the abdomen and site of insertion, are all important determinants for the rate of recovery. The authors raise the issue that “probe discomfort” may be a significant factor in trait expression. This latter concern, if correct, has
important implications for the behavioral and cardiovascular studies under way in several laboratories. How to address this concern remains unclear. The results in this paper raise important questions for all studies using telemetry probes in rodents, including which probe to employ for rats and comparably sized model organisms. The authors recommend that the smallest available probe be surgically implanted, a practice not followed currently in most laboratories. Lastly, the study also emphasizes the importance of detailing, in publications, all methods and procedures used for data acquisition.

The radiotelemetry technologies available today should provide fertile new ground for identifying and studying many complex traits and diseases, both in human and model organisms. Important in this regard are the results and conclusions from the Leon et al. paper, especially when combined with both prior studies and several additional studies winding their way through the manuscript review process. These validation and methodological publications should ensure that many of the experimental issues regarding the use of radiotelemetry would be identified; however, identification does not guarantee investigator attention to detail. Therefore, the challenge in identifying gene-trait relationships remains and is only solved by investigators using the results from studies such as the one in this issue. It is also necessary for funding agencies and academic institutions to reassert the importance of training in complex integrated systems; namely, organ system physiology, statistics, classical neurosciences, pharmacology, as well as biomedical electronics. A mouse may be treated as a “test tube” for a molecular or biochemical experiment, but for a complex trait, it must be treated as a complex, living organism. In fact, one of the greatest impacts of radiotelemetry may be in reversing the graduate educational pendulum, probably more powerful than any speech or written word. Radiotelemetry is coming of age, and if so, it is just in time!

REFERENCES


