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Exciting challenges ahead for integrative physiology

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The genetic and "omics" revolution which has so gripped biomedical research in the last decade, particularly in terms of investment in large scale infrastructure has at the same time challenged traditional areas of endeavor such as physiology. Driven by the pharmaceutical and biotech industry, high throughput "omics" platforms (genomics, proteomics, metabolomics, transcriptomics, nutrigenomics) have blossomed, providing vast arrays of information the complexity of which is requiring its own "bioinformatics" specialty area. However, each new discovery must be placed in its physiological context. From the various arrays, potential targets can be further examined with high throughput *in vitro* studies which provide the first cast of potentially relevant and important information as to the cellular context including receptor signaling and second messengers. However, realization of whether such discoveries are important as novel therapies has been problematic in the translation of these findings possibly due to insufficient or absent preclinical animal studies. This is often due to the unforeseen complexity of multicelled/organ/whole animal systems which are orders of magnitude greater than *in vitro* assays. The contribution of particular modulators thought to be important may in fact be minimal due to inbuilt redundancy or if effective, off target effects which were not predicted by the narrow focus of *in vitro* testing, precluding development of the agent further. The drivers to skip the preclinical stages of development are time and cost. However, the downside is missed opportunities and costly but ineffective clinical trials. Integrative physiologists have a critical role in both the preclinical and clinical phases of discovery but are often overlooked. Our challenge will be to make a strong case for our involvement in this process of discovery, designing and implementing appropriate experiments to truly understand the function in context.

The opportunities arising from the omic revolution are enormous and the strides in transgenics in particular have been truly remarkable. Physiologists have been reinvigorated by the arrival of an overwhelming number of new single double and triple knockout combinations of their favorite entity. The effort involved in cataloging each new and novel phenotype is actually an enormous task and perhaps beyond our current capacity. In the last few years novel tissue specific over expression, constitutively active and dominant negative variants have emerged which have given us unprecedented variety of new tools and disease models. The cre–lox system for example has opened up the possibility of eliminating specific genes in tissues by injecting the cre-recombinase. The exciting "grand" challenge for integrative physiologist will be to incorporate this new information into an expanding, ever more complex view of physiological systems. The difficulty is twofold. Firstly, choosing what to investigate is not at all simple given the complexity, the specialized nature and narrowing of focus required to extract the nuances of biological function. It can take many years of investigation to properly phenotype a mice with a single gene knockout. Resources are not limitless and qualified, trained and experienced physiologists are becoming a rare species. Secondly, the complexity within each area is not conducive to a generalist's approach in which a vast array of information needs to be expertly constructed into an "integrated" picture of physiological function. Can any one person realistically be expected to understand the intricacies of detail at the molecular, cellular, tissue organ and whole animal/human sufficiently to be able to integrate all of the contributions of the system being studied.

An excellent example of this phenomenon is the renin–angiotensin aldosterone (RAAS) system for regulation of blood pressure and fluid (blood) volume homeostasis. A Medline search of angiotensin (Ang) yields a staggering 92000, renin 47000 and aldosterone 32000 references. Components of the system include a cascade of bioactive peptides starting from the precursor angiotensinogen (1-14) and include Ang I (1-10), Ang II (1-8), Ang III (2-8), Ang (1-7), Ang IV (3-8) (Moeller et al., 1998). Enzymes involved include renin, prorennin, aminopeptidase A and N, neutral endopeptidase 24.11, prolyl endopeptidase, angiotensin converting enzyme (I and II). At the gene level there is can be important regulatory steps which for renin include promoter and enhancer sequences (Adams et al., 2006). Receptors include angiotensin receptor 1 (AT_1) which has a and b isoforms as well as AT2 receptors. The receptor for Ang IV appears to be an enzyme, insulin regulated aminopeptidase (IRAP) (Lew et al., 2003). Evolution has fashioned this system of enzymes, protein signaling molecules and receptors into performing a myriad of actions, not only the regulation of blood pressure. There are indeed many different tissue renin–angiotensin systems in addition to the kidney. A separate RAS is present in the central nervous system where in addition to regulating thirst and the sympathetic outflow and therefore blood pressure, it is involved in processing sensory information, memory, learning, pain (Raghavendra et al., 1999) mood and emotional behavior (von Bohlen und Halbach and Albrecht, 2006). RAAS may also influence the locomotor system since renin enhancer knockout mice have lower locomotor activity and angiotensin has been shown to alter the release of dopamine in the forebrain (Raghavendra et al., 1998). Interestingly, mice lacking angiotensinogen have lower spontaneous locomotor activity (Okuyama et al., 1999). Circulating angiotensin does appear to signal centrally through activation of AT_1-receptors in circumventricular organs which do not have a blood brain barrier (Davern and Head, 2007). Moreover, the areas within this barrier that are activated are also rich in AT_1-receptors. There are also many other tissues within the body

that utilize a local version of the renin–angiotensin system for example in the testes where it is involved in regulating male reproduction (Leung and Sernia, 2003). Kenneth Bernstein wrote recently "One of the great challenges scientists face is to develop a comfort level viewing biological systems and, in particular, the RAS, as part of multifactorial parallel processing." (Bernstein, 2006) This is indeed a challenge which is music to the ears of integrative physiologists who are most comfortable with multifactorial systems. The challenge is to engage and partner the transgenic specialists in productive collaborations to bring together and "integrate" new discoveries into the perspective of such parallel physiological processes and regulatory systems.

There is yet another aspect to the challenge and that relates to the fourth dimension "time". Physiological processes can be extremely fast for example protein rotational and conformational changes as well as protein–protein interactions have been measured in the nanosecond range (Boehr et al., 2006). Physiologists are well familiar with time frames of seconds, minutes and hours while ultradian and circadian processes have largely been the realm of specialists in chronobiology and biological clocks (Rhythmologists). However, physiological process are as much about development, reaching adulthood, successful reproduction, aging and transgeneration communication (genetic and epigenetic) phenomenon and finally evolution. Once again the RAAS is a noteworthy example of this dimension with for example expression of AT_1-receptor and AT_2-receptors changing between development and adulthood. RAAS is teleologically an ancient system with Ang I being present in birds, axolotl and sea lamprey (Takei et al., 2004). The latter is a 500 million year old species jawless eel like fish. Homologues of the AT_1-receptor are present in amphibians and birds but low homology with AT receptors from teleosts (ray-finned fishes) suggests there was a prototype AT receptor (Nishimura, 2001). An interesting question is whether the evolution of the RAAS which paralleled the emergence of amphibians was a major factor in dealing with salt and water balance thus enabling the transition (Nishimura, 1978).

The grand challenge therefore for integrative physiologists is to integrate the spatial and temporal components of regulatory functions at all biological levels ranging from the molecular, cellular, tissue and organs to clinical studies. "Frontiers in Integrative Physiology" will be an excellent vehicle to bring new insights into physiological processes and regulatory systems as well as their perturbation during pathological processes. Submissions which include multidisciplinary techniques and approaches and that focus on mechanisms and regulatory functions are therefore strongly encouraged.

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