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THE IMPORTANCE OF A PHYSIOLOGICAL APPROACH TO NEUROSCIENCE

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The last thirty years have witnessed a phenomenal expansion of the discipline that we now call "neuroscience". Neurophysiology, the subdiscipline of physiology concerned with the study nervous system function, has *de facto* been incorporated into neuroscience. If this phenomenon were only a matter of terminology or of "fashion", its importance would be quite limited. I am however afraid that it has also implied in many instances a decreased emphasis on the physiological perspective both for research and teaching. One of probably multiple factors that has somehow accentuated the dilution of a physiological perspective in neuroscience is the emphasis put on the study of the molecular mechanisms of nervous system development and of intracellular signaling and gene expression regulation. Not that one should be critical about these developments : quite the contrary, as they have allowed to make major progress in understanding the molecular determinants of the building of the nervous system as well as on how signaling cascades transduce signals originating outside the cell into modulation of regulatory elements of genes. This contribution is particularly significant in the field of developmental neuroscience, where genes have been identified that control particular steps in neuron migration and in nervous system construction, but neuroscience as a whole has benefited from molecular biology. The contribution of molecular tools to the understanding of nervous system cannot be sufficiently emphasized. However, we are now at a stage where the tremendous amount of data gathered thanks to the molecular approaches needs to be re-integrated into a physiological perspective of the function of the nervous system.

Neuroscience has integrated many other approaches, both conceptually and methodologically, to understand brain function in health and disease. Thus, classical disciplines such as histology, anatomy, physiology as well as biochemistry and pharmacology to name a few were integrated with psychology, computer sciences, imaging and genetics under a single banner, that of neurosciences. Of course, this has been a very important step, first, providing a common identity to scientists originating from several disciplines and secondly, it probably raised attention for support from public and private sectors. These considerations are in no way meant to be interpreted as a criticism : quite the contrary. It is indeed a natural evolution of science, where the boundaries between disciplines should be kept to a minimum and in which the drive for research should be provided by questions rather than methodological approaches or disciplinarian contexts. I would nevertheless like to emphasize the necessity to keep a strong physiological perspective in neuroscience. Indeed, since physiology can be viewed as the study of the mechanisms that maintain the homeostasis of an organism I would like to argue, that the brain is the ultimate organ for homeostasis. Indeed, our behaviours ultimately are meant to maintain our integrity and homeostasis ; these behaviours are certainly determined by subtle molecular and cellular mechanisms which involve not only the brain but also the peripheral organs. Just to give an example, think of the theory of emotions of William James, recently revisited by Antonio Damasio [1]. Perception per se does not generate an emotion. It is the associated bodily state that provides the emotional tone to the perception. The amygdala will transduce a sensory input into a change in physiological parameters, eg heart rate in the case of a fearful stimulus ; this change will be conveyed back to the brain by the interoceptive system and integration of perception and a given bodily state will occur in frontal areas. Thus, the study of the molecular mechanisms of signalling in the amygdala will greatly be enriched by considering them in an integrated physiological perspective at the organism level. I therefore plead for the importance of maintaining a physiological perspective in all aspects of current neuroscientific enquiry. In fact, keeping this physiological perspective is likely to open unexpected insights when analysing the molecular and cellular data.

I would like to provide two examples close to my field of research, which is the role of neuron-glia interactions in brain energy metabolism. Indeed, by using molecular and cellular approaches, we have characterised a mechanism whereby synaptic activity is coupled to glucose utilisation. The coupling between synaptic activity and glucose utilization (neurometabolic coupling) is a central physiological principle of brain function which has provided the basis for 2-deoxyglucose-based functional imaging with PET [2, 3]. About ten year ago we provided experimental evidence indicating a central role of astrocytes in neurometabolic coupling [4]. The basic mechanism in neurometabolic coupling is the glutamate-stimulated aerobic glycolysis in astrocytes, such that the sodium-coupled reuptake of glutamate by astrocytes and the ensuing activation of the Na-K-ATPase triggers glucose uptake and its glycolytic processing, resulting in the release of lactate from astrocytes. Lactate can then contribute to the activity-dependent fuelling of the neuronal energy demands associated with synaptic transmission. Analyses of this coupling have been extended in vivo [5], and recently have also defined the modalities of coupling for inhibitory neurotransmission as well as its spatial extent in relation to the propagation of metabolic signals within the astrocytic syncytium [6, 7]. On the basis of a large body of experimental evidence (for a recent review see [8]) we have proposed an operational model, "the astrocyte-neuron lactate shuttle". Results obtained by independent laboratories have provided further support for this model [9–11]. This body of evidence provides a molecular and cellular basis for interpreting data obtained with functional brain imaging studies. In addition, this neuron-glia metabolic coupling undergoes plastic adaptations in parallel to adaptive mechanisms that characterize synaptic plasticity. Thus, distinct subregions of the hippocampus are metabolically active at different time-points during spatial learning tasks, suggesting that a type of metabolic plasticity, involving by definition neuron-glia coupling, occurs during learning [12].

In addition, marked variations in the expression of genes involved in neuron-glia metabolic exchanges are observed during the sleep-wake cycle [13, 14]. These data suggest that glial metabolic plasticity is likely to be a concomitant of synaptic plasticity.

This analysis at a cellular and molecular level provides some insights into how neurons can provide signals to astrocytes to deliver an energy substrate when needed and where needed. Interestingly, this mechanism has now been demonstrated to operate at other levels of the central nervous system, namely, some hypothalamic nuclei and the retrotrapezoid nucleus. It is not only a curiosity of finding these mechanisms in different regions of the nervous system. The interesting part is that, at both levels, this metabolic exchange between neurons and astrocytes participates in regulatory mechanisms at the level of the entire organism. Indeed work by Rossetti and colleagues demonstrated that astrocytic derived signals, most likely lactate, is delivered to neurons in the hypothalamus to contribute to the regulation of gluconeogenesis and lipidogenesis in the liver [15, 16]. Thus, cellularly defined mechanisms when placed in the context of physiological regulation, demonstrates an impact on the whole organism homeostasis. Other findings in the retrotrapezoid nucleus by Ehlrichmann et al have shown that the release of lactate from astrocytes is key in the role of the retrotrapezoid nucleus in regulating respiration [17]. Here, we have another example where experiments designed initially to clarify exchanges at the cellular level from a pure neuroscientific perspective related to neuron-glia interaction, have provided insights into regulatory mechanisms that operate at the whole body level. I would like therefore to stress once again the importance of keeping always a physiological perspective when studying brain function even with experiments designed at the cellular and molecular levels.

It is also worth keeping in mind this perspective for teaching. I have recently been exposed to what I would call this "pseudo-dilemma" between physiology and neuroscience. In the context of the teaching of the newly established Brain Mind Institute at EPFL, we were asked to provide a basic neuroscience course for students of the technology institute who have a strong background in mathematics, physics and chemistry but less so in biology, particularly with an integrated perspective. Thus, we felt that we had to put a strong physiological bias to our neuroscience course in order to present the students with a view that would relate the facts about brain structure and function, those of a classical neuroscience course, to the physiology of the organism. To this end, we have two main parts in the course, one in which the cellular and molecular mechanisms of excitability are explored in depth ; in fact this part is strongly grounded in what we would call "General physiology". In the second part, we approach brain functions as an integral component of the maintenance of an organism's homeostasis, starting from the integrated physiological perspective and digging deep into the molecular mechanisms. In other words, in addition to the sensory and motors systems, also the mechanisms of sleep homeostasis, of memory, of neuroendocrine regulation, of emotions, of neuroenergetics, are presented emphasizing the impact of neural functions in a physiological perspective integrated at the whole body level.

The years that I spent before joining the Brain Mind Institute as a faculty and then as a chairman of a department of physiology, teaching mostly to medical students and interacting with colleagues interested in organs other that the brain, have undoubtedly influenced my perspective in approaching the study of the nervous system. I think that I have gained a lot by keeping a physiological perspective in my neuroscientific enquiry. It is my conviction that we should make all efforts to keep a physiological perspective in the teaching of neuroscience, both at the undergraduate and graduate levels. Students as well as faculty will benefit from it.

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