Hôpital Necker-Enfants Malades

In kidney transplant recipient (KTR), low blood bicarbonate level associates with reduced graft survival and mineral metabolism disorder. Yet, the relative association of blood pH and bicarbonate level with transplantation outcome or mineral metabolism disorders have not been assessed, nor the influence of blood collection site (arterial fistula *vs* peripheral vein) on bicarbonate level, which represent a specific concern in KTR. To investigate these questions we analysed blood gas parameters in a single center cohort of 1260 stable KTR, 3 months after transplantation. Inspection of PO2 distribution allowed the unambiguous identification of the arterial (i.e.: drawn from arterio-venous fistula; N=914) or venous (N=346) origin of the blood. The origin of the blood used for bicarbonate measurement was an independent predictor of bicarbonate level. In patients with arterial blood samples, 435 (46%) had bicarbonate below 22mmol/l. Among them, 196 (40%) were acidemic (blood pH < 7.38). IN multivariable analysis, acidemia associated with increased ionized calcium and phosphate level and reduced FGF23, but not with transplantation outcome. In contrast low bicarbonate levelpredicted allograft loss independently of mGFR and other potential confounders. In KTR, reduced arterial blood bicarbonate predicts outcome while acidemia is associated with altered mineral metabolism. Blood collection site should be taken into account when assessing acid-base status.

RESPIRATORY PHYSIOLOGY

Symposium

Breathing through the ages - Rhythm generation and modulatory mechanisms

Organizer: Donatella Mutolo (Firenze, Italy)

Invited Oral Presentations

OP.89

Glial and purinergic excitation of the preBötzinger complex shape the hypoxic ventilatory response

Funk GD

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The mammalian brain depends on a constant supply of oxygen to meet its energy needs. Failure of this supply for even a few minutes can result in permanent brain damage or death. A host of adaptive responses have evolved to protect brain oxygen. Prominent among these is the biphasic hypoxic ventilatory response in which an acute fall in oxygen levels (hypoxia) in the blood supplying the brain stimulates carotid body chemoreceptors, triggering a rapid (within 1 minute), Phase I increase in breathing. If oxygen levels are not restored immediately, breathing falls over the next 4-5 minutes to a lower steady state Phase II level (the secondary hypoxic respiratory depression). This secondary depression is most severe and life threatening in premature infants with apnea of prematurity (AOP). Dogma holds that the hypoxic ventilatory response results from two main processes, a peripheral chemoreceptor- mediated Phase I excitation followed by a centrally mediated depression to Phase II; i.e., the only contribution of the central nervous system to the hypoxic ventilatory response is inhibition. Recent data challenge this view with evidence that the preBötzinger Complex (preBötC), a brainstem region critical for inspiratory rhythm generation, mounts an excitatory response to hypoxia that attenuates the hypoxic respiratory depression. Specifically, astrocytes in the preBötC appear to sense hypoxia and release ATP, which in turn acts via P2Y1 receptors to excite inspiratory neurons and increase ventilation (Angelova et al. J. Neurosci. 35; 10460–73, 2015; Rajani et al. J. Physiol. online, 2017). Discussion will focus on the glial, purinergic and ionic mechanisms through which P2Y1 receptor activation excites preBötC neurons and increases ventilation in response to hypoxia. Research supported by Canadian Institutes of Health Research, Natural Science and Engineering Research Council, Canadian Foundation for Innovation and the Women and Children's Health Research Institute (University of Alberta).

OP.90

Evolutionary aspects of neural mechanisms underlying respiratory rhythm generation in vertebrates

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The lamprey, which diverged from the main vertebrate line around 560 million years ago, proved to be highly useful to identify neuronal circuits underlying rhythmic motor behaviours, such as locomotion and respiration. The isolated brainstem of the adult lamprey spontaneously generates rhythmic respiratory activity *in vitro.* The respiratory central pattern generator (CPG) is located in the paratrigeminal respiratory group (pTRG), a region rostral to the trigeminal motor

nucleus. The pTRG shows many similarities with the preBötzinger Complex (preBötC), the proposed mammalian inspiratory CPG. It is well known that ATP plays a role in the control of the preBötC and that astrocytes contribute to purinergic modulation. Recently, this issue has been investigated also in the lamprey. The results show for the first time that astrocytes strongly contribute to the maintenance of the activity of the pTRG via the glutamate-glutamine cycle. In addition, they are involved in the genesis of ATP-induced increases in respiratory frequency at the pTRG level. Acidification evokes ATP-independent increases in the respiratory motor output that requires astrocyte metabolic support. Another important neuromodulator of the preBötC is serotonin (5-HT). In the adult rabbit, 5-HT has been shown to play a pivotal role, especially through a 5-HT1A receptor-mediated inhibition of GABAergic inhibitory interneurons. The existence of a similar mechanism mediated by both GABAergic and glycinergic neurons has also been shown at the pTRG level. The results support the notion that some important features of the neural circuit underlying respiratory rhythm generation are highly conserved throughout phylogeny.

OP.91

Neuromodulation, reconfiguration and the neuronal control of breathing

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All mammals developed effective strategies to cope with reduced oxygen availability or other metabolic, environmental and behavioral challenges. An important prerequisite for survival is the necessity to be flexible and adaptive, while maintaining functional integrity during times of extreme challenges. This is particularly important for the neuronal network that controls breathing. This network is amenable to a rigorous cellular and subcellular analysis. Using modern transgenic, optogenetic and molecular techniques we identify the critical microcircuits for breathing and demonstrate that neuromodulators imbue this network with the dynamic ability to reconfigure and alter the distribution of respiratory activity within the ventral respiratory column in the brainstem. This network reconfiguration involves the differential activation and inhibition of identified excitatory and inhibitory respiratory neurons as well as glia. We also show that breathing can occur as a 1-, 2-, or 3-phase rhythm, and that every breath is assembled stochastically, with each phase being generated independently by a dedicated excitatory microcircuit. The ability of these microcircuits to reconfigure may allow breathing to remain robust, yet plastic enough to adapt not only to metabolic challenges, but also to conform to non- ventilatory behaviors such as vocalization, swallowing and coughing. Lessons learned from the respiratory network may translate to other highly dynamic and integrated rhythmic systems.

Oral Presentations

OP.92

New data on hypnic and breathing phenotype of a mouse model of down syndrome

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Down Syndrome (DS) patients commonly develop persistent sleep disorders and sleep apneas. Since the use of mouse models accelerates the understanding of DS pathophysiology, we analyzed the sleep and breathing phenotype in adult Ts65Dn mice (TS; a validated model of DS) and their controls (CTRL). Each mouse was implanted with electrodes to record electroencephalogram (EEG), neck electromyogram (nEMG) and diaphragmatic activity (DA). After 1 week, each mouse was placed in a whole-body plethysmographic (WBP) chamber for 8h during the resting (light) phase to simultaneously record breathing activity together with EEG, nEMG and DA. Based on the EEG and nEMG signals, we then discriminated wakefulness (W), non-rapid- eye-movement sleep (non-REMS) and REMS, while based on WBP signal, we checked for the occurrence of sleep apneas. The analysis of DA (still in progress) during apneic events will allow to discriminate between central and obstructive sleep apneas. Preliminary data (TS = 5, CTRL = 3) show that TS mice spent less time in W and more time both in non-REMS and REMS compared to CTRL. Moreover, TS mice showed fragmentation of W and non-REMS while, during REMS, they tended to have more sleep apneas than CRTL. These preliminary results corroborate previously published data on excessive sleep time in TS mice while reporting completely new findings on wake-sleep cycle fragmentation and increased sleep apnea episodes during REMS. These results lay the ground to understand the neural and molecular pathways of sleep and breathing alteration in DS.