Biology and Pathology

Central Nervous System

Pathophysiology and Imaging of Stroke

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Learning Objectives:

- The audience will learn about the pathophysiological cascade of events following a stroke
- The audience will learn to discriminate the different relevant phases of pathophysiological developments in the acute, subacute and chronic time window following the ischemic incident
- The audience will learn the prerequisites to study stroke and to assess therapeutic strategies in the experimental field, with focus on translational relevance. This includes animal models, experimental monitoring of animal status, tool to investigate various aspects, and assessment of therapeutic effectiveness of approaches

The different forms of stroke – ischemic and hemorrhagic – will be discussed and their clinical relevance. This will have substantial influence on the optimal choice of animal model for the investigation on ideal treatment. Directly following the primary event of an occluded (ischemic case) or ruptured (hemorrhagic case) vessel, a series of pathophysiological events take place being the cause for the final tissue loss and the clinically relevant functional deficit. These cascades of events are divided into various phases, beginning with the acute phase during which the metabolic disturbance will lead to anaerobic glycolysis, tissue acidosis, and finally electric silence of the neuronal cellular network. This will result in tissue necrosis (and apoptosis to minor ex tent) within several hours if reperfusion and nutrient supply are not rapidly restored. The second phase includes secondary toxic events caused by toxic molecules as result of the anaerobic metabolic disturbance and intracellular imbalance. The next phase lasts for 1–2 weeks and is best characterized by inflammation as response to the tissue loss. Macrophages from the vascular system will invade the lesioned territory, followed by activated microglia to take care of the dead cell debris and to seal the lesion against the healthy tissue by a gliosis scar reaction. In a later phase, a second round of inflammatory reaction is discussed, considered to be predominantly constructive and supportive in regenerative processes. This leads to the final phase, the potential regeneration phase. Here we will discuss mechanisms of action, both of endogenous processes as well as therapeutic approaches. Of course, also a delayed destructive process is still active during this time window: contributions from delayed retrograde degeneration which will affect remote tissue areas originally untouched by the primary ischemic event.

We will present animal models best suited for the investigation of appropriate therapeutic interventions to these above-mentioned phases of pathophysiological events. In this context, the tools to describe, monitor and assess the various steps of pathophysiological events will be presented, with focus on using invasive and noninvasive imaging modalities, doing justice to the fact that stroke represents a regionally heterogeneous process which consequently requires a region-resolved characterization of the relevant processes.

Finally, assessment of functional deficit and functional improvement will be discussed in the quest for outcome improvement during therapeutic interventions. Furthermore, the pitfalls in the assessment of functional improvement in the animal model will be discussed when using behavioral test batteries. Here, often times, care is needed to distinguish between compensation for lost function and true functional improvement. Here again, the role of noninvasive imaging, particularly fMRI and functional connectivity fMRI will be presented.