In ischemic stroke, vascular occlusion and energy deficit rapidly induce tissue infarct. Cell damage propagates to surrounding tissues for several hours. This therapeutic window provides time to save neuronal cells in penumbra. To determine proteins involved in neurodegeneration and neuroprotection in penumbra, we studied protein expression profile in 2 mm ring around photothrombotic infarct core induced in rat cerebral cortex by local laser irradiation after rose bengal administration. Histological and ultrastructural studies showed edema and degeneration of neurons, glia and capillaries, which decreased gradually across penumbra. Expression profile of 224 signalling proteins, 1, 4 or 24 hours after photothrombotic infarct comparing with untreated contralateral cortex was studied with antibody microarrays. Diverse cellular subsystems were involved in penumbra response. Proteomic analysis showed concerted upregulation of diverse proteins that initiate, regulate and execute apoptosis (Par4, E2F1, p75, p38, JNK, p53, GADD153, GAD65/67, NMDAR2a, c-myc, Bcl-10, AIF, SMAC/DIABLO, PSR, caspases 3, 6 and 7). Different anti-apoptotic (Bcl-x, p63, p21WAF-1, MDM2, ERK5, MKP-1, NEDD8) and signalling proteins that regulate cell metabolism, functions and survival (calmodulin, CaMKIIα, CaMKIV, ERK1/2, MAKAPK2, PKCa, PKCβ, PKCμ, RAF1, protein phosphatase 1α, ATF2, estrogen and EGF receptors) were simultaneously overexpressed. Bidirectional changes in adhesion and cytoskeleton proteins were associated with penumbra destruction or remodelling. Proteins that regulate actin cytoskeleton (cofilin, actopaxin, p120CTN, α-catenin, p35, myosin Va, pFAK) were up-regulated, whereas others (ezrin, tropomyosin, spectrin (α+β), βIV-tubulin, polyglutamated β-tubulin, cytokeratins 7 and 19) were downregulated. Downregulation of syntaxin, AP2β/γ, and adaptin β1/2 indicated impairment of vesicular transport and synaptic processes. Downregulation of Cdk6, Cdc7 kinase, Trf1, and topoisomerase-1 showed suppression of proliferation. APP, nicastrin and β-amyloid were upregulated. These data provide integral view on neurodegeneration or neuroprotection processes in penumbra. Some of these proteins may be potential targets for anti-stroke therapy.

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