Summary

The ubiquitin-proteasome system (UPS) and autophagy are two major pathways to degrade misfolded proteins that accumulate under pathological conditions. When UPS is overloaded, the degeneration pathway may switch to autophagy to remove excessive misfolded proteins. However, it is still unclear whether and how this switch occurs during cerebral ischemia. In the present study, transient middle cerebral artery occlusion (tMCAO) resulted in accelerated ubiquitinpositive protein aggregation from 0.5 h of reperfusion in mice brain after 10, 30 or 60 min of tMCAO. In contrast, significant reduction of p62 and induction of LC3-II were observed, peaking at 24 h of reperfusion after 30 and 60 min tMCAO. Western blot analyses showed an increase of BAG3 and HDAC6 at 1 or 24 h of reperfusion that was dependent on the ischemic period. In contract, BAG1 decreased at 24 h of reperfusion after 10, 30 or 60 min of tMCAO after double immunofluorescent colocalization of ubiquitin, HSP70, p62 and BAG3. These data suggest that a switch from UPS to autophagy occurred between 10 and 30 min of cerebral ischemia depending on the BAG1/BAG3 ratio and level of HDAC6.