A depressive or hibernation-like effect of chlorpromazine and promethazine (C + P) on brain activity was reported to induce neuroprotection, with or without induced-hypothermia. However, the underlying mechanisms remain unclear. The current study evaluated the pharmacological function of C + P on the inhibition of neuroinflammatory response and inflammasome activation after ischemia/reperfusion. A total of 72 adult male Sprague-Dawley rats were subjected to 2 h middle cerebral artery occlusion (MCAO) followed by 6 or 24 h reperfusion. At the onset of reperfusion, rats received C + P (8 mg/kg) with temperature control. Brain cell death was detected by measuring CD68 and myeloperoxidase (MPO) levels. Inflammasome activation was measured by mRNA levels of NLRP3, IL-1β, and TXNIP, and protein quantities of NLRP3, IL-1β, TXNIP, cleaved-Caspase-1, and IL-18. Activation of JAK2/STAT3 pathway was detected by the phosphorylation of STAT3 (p-STAT3) and JAK2 (p-JAK2), and the co-localization of p-STAT3 and NLRP3. Activation of the p38 pathway was assessed with the protein levels of p-p38/p38. The mRNA and protein levels of HIF-1α, FoxO1, and p-FoxO1, and the co-localization of p-STAT3 with HIF-1α or FoxO1 were quantitated. As expected, C + P significantly reduced cell death and attenuated the neuroinflammatory response as determined by reduced CD68 and MPO. C + P decreased ischemia-induced inflammasome activation, shown by reduced mRNA and protein expressions of NLRP3, IL-1β, TXNIP, cleaved-Caspase-1, and IL-18. Phosphorylation of JAK2/STAT3 and p38 pathways and the co-localization of p-STAT3 with NLRP3 were also inhibited by C + P. Furthermore, mRNA levels of HIF-1α and FoxO1 were decreased in the C + P group. While C + P inhibited HIF-1α protein expression, it increased FoxO1 phosphorylation, which promoted the exclusion of FoxO1 from the nucleus and inhibited FoxO1 activity. At the same time, C + P reduced the co-localization of p-STAT3 with HIF-1α or FoxO1. In conclusion, C + P treatment conferred neuroprotection in stroke by suppressing neuroinflammation and NLRP3 inflammasome activation. The present study suggests that JAK2/STAT3/p38/HIF-1α/FoxO1 are vital regulators and potential targets for efficacious therapy following ischemic stroke [1)].

1)
Guo S, Geng X, Lee H, Ding Y. Phenothiazine Inhibits Neuroinflammation and Inflammasome Activation Independent of Hypothermia After Ischemic Stroke. Mol Neurobiol. 2021 Aug 29. doi: 10.1007/s12035-021-02542-3. Epub ahead of print. PMID: 34455546.