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Trifluoromethyl Ketones Show Culture Age-dependent Inhibitory Effects on Low K⁺-induced Apoptosis in Cerebellar Granule Neurons

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We previously reported that two trifluoromethyl ketones, 3,3,3-trifluoro-1-phenyl-1,2-propanedione (TF1) and 1,1,1-trifluoro-3-phenyl-2-propanone (TF2), have neuroprotective effects against low K⁺-induced apoptosis in cerebellar granule neurons (CGNs) exposed at 12-13 days in vitro (DIV). On the other hand, these compounds showed weak neuroprotective potency against 7 DIV CGNs. It is reported that actinomycin D (Act-D), cycloheximide (CHX), and caspase-3 inhibitors prevent the apoptosis of CGNs induced by K⁺ deprivation. However, these experiments are generally performed using 7 DIV CGNs. We investigated and compared the anti-apoptotic efficacy of these drugs and newly discovered TF1 and TF2 to protect DIV 7 and 12-13 CGNs from death induced by K⁺ deprivation. Apoptosis of CGNs induced by K⁺ withdrawal at 13 DIV was potently inhibited by Act-D and CHX similar to those at 7 DIV. Caspase-3 inhibitors moderately suppressed cell death during lowK⁺-induced apoptosis both exposed 7 and 13 DIV. Serine protease inhibitor N-tosyl-L-phenylalanyl chloromethylketone (TPCK) had no effect on K⁺-deprivation-induced apoptosis of CGNs at both 7 and 12 DIV. This study shows that there are different pathways of apoptosis in CGNs depending on the culture age.