SELECTIVE REGULATION OF [^{3}H]D-ASPARTATE RELEASE FROM HIPPOCAMPAL NERVE ENDINGS BY LARGE-CONDUCTANCE CA^{2+}- AND VOLTAGE-ACTIVATED K^+ (BK) CHANNELS

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Large-conductance Ca^{2+}- and voltage-activated K^+ (BK) channels provide a dual detector of neuronal activity since they can be activated by both membrane potentials and by an increased intracellular concentration of Ca^{2+} ions. BK channels have been identified in various tissues, with most studies concentrating on their distribution in smooth muscle cells, where they control vascular smooth muscle relaxation and in neurons, where they contribute to the regulation of neurotransmitters release. However, the differential role of BK channels in the regulation of the release of excitatory and inhibitory neurotransmitters from central neurons is yet unknown. In this study, we have addressed this question by investigating the effect of drugs able to inhibit or to enhance the activity of BK channels on the K^+-evoked release of [^{3}H]-labeled neurotransmitters from perfused synaptosomes isolated from specific rat brain areas. Iberiotoxin (IbTX) (0.1-30 nM), a neurotoxic peptide derived from the venom of the *Buthus tamulus* scorpion, dose-dependently increased the 15 mM K^+-evoked release of the labeled glutamate analog, [^{3}H]D-aspartate ([^{3}H]D-ASP), from rat hippocampal synaptosomes. The highest concentration tested (30 nM) produced an increase of 1.80±0.10%, with an EC_{50} of 1.96±0.13 nM, which is consistent with the K_D values on BK channels obtained in electrophysiological and biochemical studies. K^+-evoked [^{3}H]D-ASP release from hippocampal synaptosomes was also increased by paxilline (PAX; 0.01-1 µM), an indole alkaloid that blocks BK channel with an higher degree of selectivity when compared to IbTX, which acts as a blocker also of other voltage-gated K^+ conductances. The lowest effective concentration of PAX was 10 nM, and the highest concentration tested (1 µM) increased release by 1.60±0.09%. The selective involvement of BK channels in the effects of IbTX and PAX was also suggested by the fact that NS1619 and BMS 204352, two compounds known to activate BK currents, in doses ranging from 1 to 30 µM, both produced a concentration-dependent inhibition of [^{3}H]D-ASP release with E_{max} of 55 ± 3.85% ($p<0.01$, n=9) and 66 ± 3.95% ($p<0.01$, n=8), respectively. By contrast, IbTX had no effect on [^{3}H]-noradrenaline release from synaptosomes isolated from the cerebral cortices, hippocampi, or hypothalami, as well as on [^{3}H]-GABA release from cortical or hippocampal synaptosomes, or on [^{3}H]-dopamine release from striatal synaptosomes. These findings provide evidence that BK channels selectively regulate glutamate release from hippocampal glutamatergic nerve endings, and suggest that BK channel activators might prove useful for limiting excitotoxic damage to neurons associated with ischemic insults and other conditions characterized by excessive glutamate release.