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Title: Growth Inhibition by Bupivacaine Is Associated with Inactivation of Ribosomal Protein S6 Kinase 1

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Abstract

Bupivacaine is an amide type long acting local anesthetic used for epidural anesthesia and nerve blockade in patients. Use of bupivacaine is associated with severe cytotoxicity and apoptosis along with inhibition of cell growth and proliferation. Although inhibition of Erk, Akt, and AMPK seemingly appears to mediate some of the bupivacaine effects, potential downstream targets that mediate its effect remain unknown. S6 kinase 1 is a common downstream effector of several growth regulatory pathways involved in cell growth and proliferation known to be affected by bupivacaine. We have accordingly attempted to relate the growth inhibitory effects of bupivacaine with the status of S6K1 activity and we present evidence that decrease in cell growth and proliferation by bupivacaine is mediated through inactivation of S6 kinase 1 in a concentration and time dependent manner. We also show that ectopic expression of constitutively active S6 kinase 1 imparts substantial protection from bupivacaine induced cytotoxicity. Inactivation of S6K1 though associated with loss of putative mTOR mediated phosphorylation did not correspond with loss of similar phosphorylations in 4EBP1 indicating that S6K1 inhibition was not mediated through inactivation of mTORC1 signaling pathway or its down regulation.

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