Inducing Central Sensitization with SP-CTA

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molecular pathways simultaneously. To selectively stimulate the cAMP pathway we chose to use cholera toxin. Cholera toxin stimulates cAMP production by ADP-ribosylating Gs, which then stimulates adenylate cyclase [23]. By chemically coupling substance P to the C-terminus of the A subunit (catalytic subunit) of cholera toxin (SP-CTA) we were able to target the CTA specifically to NK1 receptor-expressing cells [24]. Figure 1 illustrates the uptake of SP-CTA into rat cervical dorsal horn neurons following an intracisternal injection. The section is co-labeled with antibodies to NK1 receptors demonstrating co-localization of the toxin and receptors. The conjugate was not observed in any neurons or cells that did not express NK1 receptors.

In a series of experiments we tested SP-CTA on behavior following intrathecal administration to rats. Doses from 0.3 to 3 μg produced significant sensitization to thermal stimuli on the hind paws of rats 24 hours following the injections. Interestingly, with higher doses the sensitization appeared to be suppressed [24]. These findings suggested that descending inhibitory pathways were activated by the SP-CTA-induced sensitization. Preliminary data indicate that the opioid antagonist naloxone can suppress the descending inhibitory control induced by SP-CTA, exposing profound hypersensitivity to thermal stimuli (data not shown). These findings support the hypothesis that descending control systems are activated by the actions of SP-CTA on spinal cord and brain stem NK1 receptor-expressing neurons.

In summary, SP-CTA is an exciting new tool to examine the function of neurons that possess neurokinin receptors in the central nervous system. The agent selectively enters these neurons through the NK1 receptors and stimulates the production of cAMP for up to three days [24]. As revealed by our studies novel cell functions can be found through this form of selective neuronal stimulation.

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