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Stimulatory Mechanisms of Neurite Outgrowth by Activation of Cl^- Transporters

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Summary

We have recently reported that $Na^+/K^+/2Cl^-$ cotransporter isoform 1 (NKCC1) plays an essential role in nerve growth factor (NGF)-induced neurite outgrowth in PC12D cells. On the other hand, it has been reported that dietary flavonoids, such as quercetin, apigenin, and luteolin, stimulate various ion transporters. In the present report, we investigated the effect of quercetin, a flavonoid, on NGF-induced neurite outgrowth in PC12 cells (the parental strain of PC12D cells). Quercetin stimulated the NGF-induced neurite outgrowth in a dose-dependent manner. Knock down of NKCC1 by RNAi methods abolished the stimulatory effect of flavonoid. Quercetin stimulated NKCC1 activity (measured as bumetanide-sensitive ^{86}Rb influx), without any increase in the expression level of NKCC1 protein. The stimulatory effect of quercetin on neurite outgrowth was depended upon extracellular Cl^-. These observations indicate that quercetin stimulates the NGF-induced neurite outgrowth via an increase in Cl^- incorporation into the intracellular space by activating NKCC1 in PC12 cell.