RELEASE OF [3H]GABA EVOKED BY HIGH AFFINITY GABA UPTAKE THROUGH GAT1 TRANSPORTERS OCCURS BY HOMOEXCHANGE AND THROUGH GAT1-INDEPENDENT, CA2+-MEDIATED MECHANISMS

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High-affinity uptake of GABA into nerve terminals may have functions other than recapture of the neurotransmitter. Synaptosomes purified from mouse cerebellum were prelabelled with [3H]GABA and then superfused with GABA and drugs selective for some presynaptic targets. Influx of GABA through GAT1 transporters stimulated efflux of [3H]GABA in a concentration-dependent manner (EC50 ~ 3 μM). The efflux of the transmitter occurred in part by GAT1 reversal through the so called homoexchange. The ion fluxes (particularly Na+ influx) accompanying GABA uptake triggered intraterminal Ca2+ signals through both plasmalemmal Na+/Ca2+ exchangers, sensitive to KB-R7943 or to ifenprodil and mitochondrial Na+/Ca2+ exchangers, sensitive to CGP37157. These Ca2+ signals likely facilitated GABA release from nerve terminals via niflumic acid- and NPPB-sensitive anion channels. The results show that GABA, at concentrations corresponding to the high-affinity uptake, can evoke GABA release which occurs in part by the expected GAT1-mediated homoexchange, while the transporter-independent component of the GABA uptake-evoked GABA release takes place by hitherto unsuspected mechanisms which include Na+/Ca2+ exchangers and anion channels. The significance of the novel function of the GABA high-affinity uptake here identified deserves further multidisciplinary investigation.