GLUTAMATE RELEASE INDUCED BY ACTIVATION OF GAT-1 TRANSPORTERS SITED ON GLUTAMATE RELEASING SPINAL CORD GLIOSOMES AND ITS AUGMENTATION IN A MOUSE MODEL OF AMYOTROPHIC LATERAL SCLEROSIS

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Co-localization of transporters able to recapture the released transmitter (homotransporters) or to selectively take up transmitters/modulators originating from neighbouring structures (heterotransporters) has been demonstrated to occur in a same axon terminal in several neuronal phenotypes. Activation of terminal heterotransporters leads to the release of the transmitter specific of the terminal in point. It is widely accepted that GABA transporters are situated not only on neuronal terminals but also on astrocytes where they mediate GABA uptake. We have previously demonstrated the presence of release-regulating GABA heterotransporters on glutamatergic spinal cord nerve terminals. We here used purified preparations of astrocyte-derived subcellular particles (gliosomes) (1) to study whether this phenomenon also occurs in glial cells. Spinal gliosomes accumulated [^{3}H]D-Asp through GLAST and GLT1 transporters and, when exposed to GABA, they released the radioactive tracer or endogenous glutamate (Glu) in a receptor-independent manner, as a consequence of GABA penetration through its selective transporters into Glu releasing particles. The GABA-evoked Glu release was neither exocytotic nor carrier-mediated, in nature, but it involved volume-activated chloride channels, through which glutamate can be exported from gliosomes. These functional results were supported by confocal microscopy analysis showing co-expression of GAT1 and GLAST or GLT1 in GFAP-positive gliosomes. Interestingly, the effect of GABA was up-regulated in gliosomes prepared from the spinal cord of a mouse model of amyotrophic lateral sclerosis, leading to an over-release of [^{3}H]DASP. To conclude, in mice spinal cord, transporters for GABA and for Glu coexist on the same glial cell. Activation of the GABA transporters elicits Glue release and this mechanism may play a role in the Glu-mediated excitotoxicity reported to play a role in the pathogenesis of this motor neuron disease. (Supported by grants from Italian Ministry of University).

(1) Stigliani S. Zappettini S., Raiteri L., Passalacqua M., Melloni E., Venturi C., Tacchetti C, Diaspro A., Usai C., Bonanno G., J. Neurochem. (2006) 96: 656-668.