THE HUMAN IMMUNODEFICIENCY VIRUS-1 PROTEIN (TAT) MODULATES NMDA RECEPTOR FUNCTION BY ACTING AT COLOCALIZED METABOTROPIC GLUTAMATE RECEPTOR 1

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We investigated the effects of the human immunodeficiency virus-1 transactivator of transcription (Tat) on the release of noradrenaline (NA) from human and rat brain synaptosomes. Tat could not evoke directly release of [^{3}H]NA. In the presence of Tat (1 nM), N-methyl-D-aspartate (NMDA) concentrations unable to release (human synaptosomes) or slightly releasing (rat synaptosomes) [^{3}H]NA became very effective. The NMDA/Tat-evoked release depends on NMDA receptors (NMDARs) since it was abolished by MK-801 (dizocilpine). Tat binding at NMDARs was excluded. The NMDA-induced release of [^{3}H]NA in the presence of glycine was further potentiated by Tat. The release evoked by NMDA/glycine/Tat depends on metabotropic glutamate receptor 1 (mGluR1) activation, since it was halved by mGluR1 antagonists. Tat seems to act at the glutamate recognition site of mGluR1. Recently, Tat was shown to release [^{3}H]acetylcholine from human cholinergic terminals; here, we demonstrate that this effect is also mediated by presynaptic mGluR1. The peptide sequence Tat41-60, but not Tat61-80, mimicked Tat. Phospholipase C, protein kinase C, and cytosolic tyrosine kinase are involved in the NMDA/glycine/Tat-evoked [^{3}H]NA release. To conclude, Tat can represent a potent pathological agonist at mGlu1 receptors able to release acetylcholine from human cholinergic terminals and up-regulate NMDARs mediating NA release from human and rat noradrenergic terminals.

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