Psychoactive drugs impact on the epigenetic machinery of neural cells

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INTRODUCTION
In recent years several studies indicated that apart from targeting classical neurotransmitter circuits, certain psychoactive drugs impact on the epigenetic signature of neural cells. We lately showed that treatment of primary cortical astrocytes with the antidepressant amitriptyline reduces genomewide CCGG methylation which was accompanied by a decrease in DNA methyltransferase activity. We now analysed this phenomenon in more detail.

RESULTS
Treatment of astrocytes with antidepressants (ADs) leads to a reduction of DNA methyltransferase (DNMT) activity in an indirect manner. (A) Nuclear extracts from primary cortical astrocytes, which had been treated with the indicated drugs for 72 hr, were prepared and DNMT activity was measured using the methylicon donor S-adenosyl-L[methyl-3H]-methionine and Poly(dI-dC)-Poly(dI-dC) as a DNA substrate. All drugs in (A) were used at a concentration of 10 µM, except CBZ (100 µM) and VPA (10 mM). (B) DNMT activity of astrocytic nuclear extracts supplemented with 10 µM AMI was determined. (CBZ, carbamazepine; VPA, valproic acid; CIT, citalopram; PAR, paroxetine; VEN, venlafaxin; DES, desipramine; IMI, imipramine; AMI, amitriptyline). Control has been set to 100%.

The effect of AMI and PAR on DNMT activity is cell type, concentration and time dependent. (A) DNMT activity was measured in nuclear extracts from primary cortical neurons, neural stem cells (NSC) and C6 glioma cells after treatment with 5 µM (Neurons) or 10 µM (NSC and C6) AMI or PAR for 72 hr. Primary cortical astrocytes were incubated with the indicated concentrations of AMI for 72 hr (B), or with 10 µM AMI for 24 and 48 hr (C) and DNMT activity was determined. Control has been set to 100%.

CONCLUSION
We could show that AD treatment decreases DNMT1 activity in primary cortical astrocytes in an indirect manner and without changing mRNA or protein levels of DNMT1. We hypothesise that long-term treatment with antidepressants impacts on chromatin remodeling processes, ultimately leading to persistent changes in gene expression patterns.