

Increased cortico-striatal uptake of dopamine as a potential mechanism of antipsychotic failure

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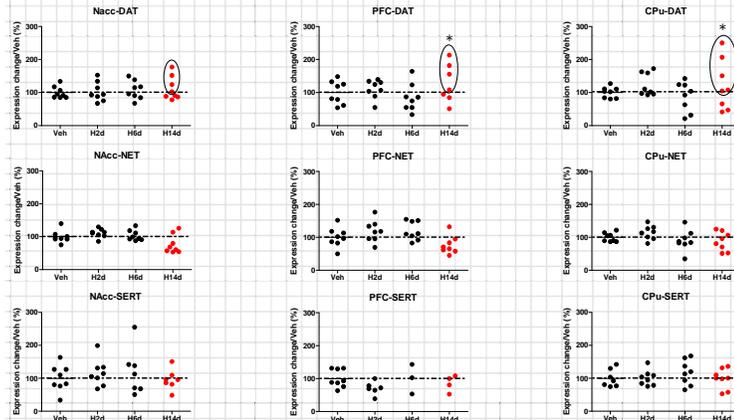
Neurotransmitter transporter changes after haloperidol treatment

Introduction:

Antipsychotic failure is a common consequence of chronic treatment in schizophrenia [1]. The neurobiology of treatment failure is unknown. Animal models have captured antipsychotic failure after 14 days continuous treatment with osmotic pumps [2,3]. Dopamine D2 receptor supersensitivity it is not sufficiently explicative of treatment failure [2]. Numerous pre-clinical studies unambiguously report that 2-3 weeks antipsychotic treatment leads to a decrease of extracellular dopamine basal levels in the striatum. We found this to occur specifically during treatment failure, but not during treatment efficacy, in an animal model [3]. Decreased extracellular dopamine basal levels lead to a decreased homeostatic negative feedback. It may potentiate dopamine signalling by keeping on the release of dopamine, which might overwhelm antipsychotic inhibition and eventually causes treatment failure.

We enquired whether antipsychotic induced-decrease of dopamine basal levels might be due to an 1) increased dopamine transporter activity, 2) decreased dopamine synthesis or 3) decreased release capacity.

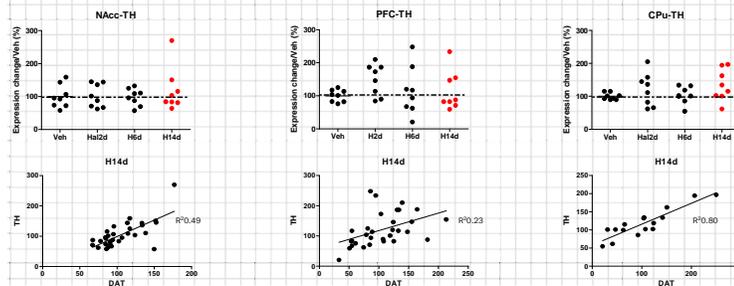
To respond these enquiries, we measured 1) the monoamine transporters and 2) tyrosine hydroxylase (TH) concentrations at different intervals of haloperidol treatment as an index of dopamine uptake and synthesis changes, respectively. 3) Then, we measured dopamine release after local potassium (K+) infusion in target brain areas during treatment failure.



Dopamine synthesis capacity after haloperidol treatment

Methods:

Western-blotting: dopamine, serotonin, noradrenalin transporters (DAT, SERT, NET) and TH expressions were measured in nucleus accumbens (NAcc), caudate-putamen (CPU) and medial prefrontal cortex (PFC) specimens from control and haloperidol treated rats (n=8/group), after 2, 6 and 14 days treatment. Protein levels were measured in the synaptosomal fractions (DAT, SERT) as well as in total extracts (DAT, NET). Microdialysis: Extracellular dopamine was sampled from NAcc, CPU and PFC in vehicle and haloperidol treated (0.5mg/kg/d, 14 days) rats (n=5/group) before and after an infusion (via reversed dialysis) of 100mM K+. HPLC was used for dopamine quantification. We also measured the extracellular concentrations of haloperidol before and after potassium infusion in caudate-putamen and medial prefrontal cortex (n=5) with GC-MS. The DA uptake rate was also measured according to the following formula: %baseline peak/min to recovery baseline (after K+ treatment).

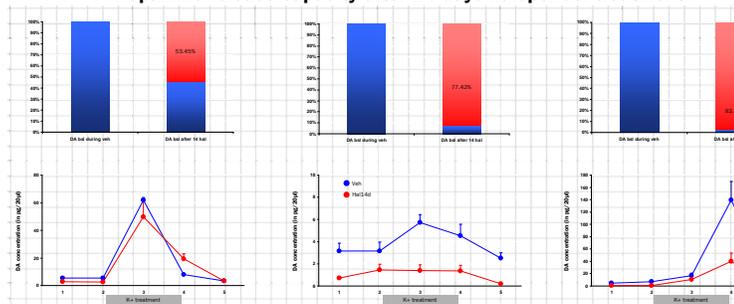


Dopamine release capacity after 14 days haloperidol treatment

Results:

Fourteen days haloperidol treatment increased DAT expression in the cortico-striatal network compared to vehicle (P=0.015). DAT was increased in a subgroup of rats (median split) in the CPU and PFC (P<0.05). TH levels were increased as a function of DAT levels after 14 days haloperidol treatment in the 3 brain regions (P<0.01).

Fourteen days haloperidol treatment reduced basal dopamine in the CPU and PFC (P<0.05). A trend was also observed in NAcc (P=0.06). Potassium infusion induced dopamine release in control and haloperidol treated rats in CPU and NAcc (P<0.05), with no between-group differences in the NAcc (P>0.05). Surprisingly, we found that also haloperidol was released after local K+ challenge (P<0.05). After haloperidol treatment the uptake of dopamine was not increased (P>0.05), although it increased the variance in the uptake rate among each animal (Table 1 and 2, P<0.0001). Within the haloperidol treated group, the dopamine uptake rate was different in the 3 brain regions according to the following order: CPU > NAcc > PFC (Table 2).



Discussion:

After fourteen days haloperidol treatment, a time point when the drug was reported to fail in animal models, we found evidence for an up-regulation in the dopamine transporter in the cortico-striatal network. Also the dopamine uptake was increased. This adaptation to haloperidol treatment can lead to a decreased dopamine basal levels. This hypothesis might be supported by the neuronal haloperidol (exogenous ligand) release from CPU and PFC, which were reported here to have the major share in the increase of DAT expression. These effects were accompanied by increased TH levels, which keep up the availability of ready-to-release dopamine. We suggest that the adaptations observed here, together with the well known D2 supersensitivity, might offer the ground to better understand the neurobiological mechanisms of antipsychotic action and failure.

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