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ORIGINAL PAPER

Protective effects of haloperidol and clozapine on energy-deprived OLN-93 oligodendrocytes

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Abstract Magnetic resonance imaging and postmortem studies on schizophrenia provided evidence for compromised myelin integrity and reduced numbers of oligodendrocytes, which may worsen during the disease course. However, it is not clear whether these findings result from disease-inherent oligodendrocyte degeneration or side effects of antipsychotic treatment. Therefore, effects of haloperidol and clozapine on the viability and apoptosis of immature oligodendrocytes (OLN-93 cells, immunopositive for NG2, Olig1, Olig2) have been evaluated in the present study by labeling with propidium iodide and a caspase 3 assay. Given the indications for impaired cerebral energy supply in schizophrenia, a serum and glucose deprivation (SGD) model was chosen in comparison with the basal condition (BC). SGD led to increased necrotic and apoptotic cell death. Haloperidol and clozapine were partially protective in this model and reduced the percentage of propidium iodide–positive cells, while caspase 3 activity was not altered. No significant drug effects were observed under BC. The observed protective effects of haloperidol and clozapine on energy-deprived OLN-93 oligodendrocytes suggest that previously reported reductions in oligodendrocyte density in schizophrenia are rather disease related than a side effect of medication. A new mechanism of antipsychotic action is suggested, which may help to establish new oligodendrocyte-directed therapies of schizophrenia.

Keywords Schizophrenia · Oligodendrocytes · OLN-93 cells · Clozapine · Haloperidol

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Introduction

Schizophrenia is increasingly conceptualized as an illness of disturbed functional circuitry, and cerebral inter- and intra-hemispheric disconnectivity has been suggested to play a major role as an early event in the disease course [1, 15]. A wide range of white matter abnormalities have been revealed in schizophrenia. They include global and focal volume reductions, reduced fractional anisotropy, and alterations in density as well as morphology and gene expression profiles of the myelin-forming oligodendrocytes (OLs) and their progenitors [2, 5, 18, 31]. Myelinated structures are a candidate anatomical substrate for disconnectivity, since myelin is important for the rapid axonal conductance and information flow between distant brain areas. Decreases in OL density in schizophrenia (up to 30% in some brain areas), altered spatial distribution, and altered cell morphology are indeed key findings in the

neuropathology of schizophrenia [11, 32]. Reduced OL density in schizophrenia is not restricted to white matter, but may also occur in gray matter areas, e.g., the neocortex and hippocampus [11, 28, 34]. Cytomorphological abnormalities were reported, such as an increased density of nuclear heterochromatin as well as dystrophy, necrosis and apoptosis of OLs, and swelling of periaxonal OL processes [32]. In spite of these advances in human studies, there is little information available from cell culture and animal studies that could help to clarify the putative role of OLs in the pathogenesis and treatment of schizophrenia.

Recent publications are pointing to schizophrenia-related disturbances in glucose metabolism not only in medicated patients but also in drug-naïve cases and unaffected first-degree relatives [7, 27, 37]. In vivo fluorodeoxyglucose positron emission tomography (FDG-PET) studies showed state-dependent alterations in cerebral glucose metabolism and functional disconnection, e.g., of the prefrontal cortex, thalamus, and mediotemporal lobe [10, 22]. Moreover, increased concentrations of glucose were found in the cerebrospinal fluid of first-onset and prodromal schizophrenia patients [12, 13]. This finding may indicate impaired cerebral glucose uptake, for example by impaired local insulin signaling via AKT and GSK3, as suggested by postmortem studies in dorsolateral prefrontal cortex and hippocampus tissue from patients with schizophrenia [6, 20, 40]. Proteomic, metabolomic, and microarray studies of human brain tissue give even more support to the hypothesis of a dysfunctional energy metabolism in schizophrenia brains [19, 21, 25].

The above-mentioned studies provide evidence for compromised myelin and OL integrity along with reduced numbers of OLs in schizophrenia. However, it is uncertain whether OL degeneration rather reflects disease-inherent mechanisms or effects of antipsychotic treatment. Therefore, we aimed to evaluate the action of the typical antipsychotic haloperidol and the atypical prototype drug clozapine on the viability of OLN-93 oligodendrocytes by labeling with propidium iodide and a caspase 3 assay. The OLN-93 cell line was established by Richter-Landsberg et al. [26]. It expresses a broad range of markers (NG2, CNP, MAG, MOG, PLP) and can be situated due to its electrophysiological features at a developmental stage between a late pre-oligodendrocyte and a late immature oligodendrocyte, regardless of serum concentration [3]. Moreover, OLN-93 cells are expressing 5HT1A and 5HT2A serotonin receptors, D2, D3, and D4 dopamine receptors and the muscarinic M4 acetylcholine receptor, which are modulated by antipsychotic drugs [30]. Given the indications for impaired cerebral energy supply in schizophrenia, a serum and glucose deprivation (SGD) model was chosen in comparison with the basal condition (BC) of unrestricted energy supply.

Materials and methods

Cell culture

Oligodendroglial OLN-93 cells were kept as previously described [30]: Cryopreserved OLN-93 cells were defrosted, resuspended in DMEM supplemented with 10% fetal calf serum, 50 U/ml penicillin, and 50 µg/ml streptomycin (growth medium), and transferred to culture flasks. After 1 week, cells were removed by mild trypsinization (5 min; trypsin/EDTA: 0.05%/0.002%) and replated (5×10^4 cells/∅35-mm Petri dish for immunocytochemistry and propidium iodide/fluorescein diacetate labeling; 8×10^{10} cells/50-ml flask for the caspase 3 assay). After 3 days, the fetal calf serum concentration of the growth medium was reduced to 0.5%, and the respective experiments were carried out 72 h later.

Given the therapeutic plasma levels of haloperidol (5–20 ng/ml) and clozapine (100–600 ng/ml) with 10- to 30-fold higher levels in brain tissue, effects of antipsychotic medication were analyzed by adding vehicle (phosphate-buffered saline, PBS), 0.1 and 1 µg/ml haloperidol or 1 and 10 µg/ml clozapine to the cell culture [38]. For SGD, the normal growth medium was replaced by serum- and glucose-free DMEM for 24 h. All cultures were kept at 37°C in a humidified atmosphere under 5% CO2 in air (normoxic conditions) for the duration of the experiment.

Immunocytochemistry

OLN-93 cells were washed twice with phosphate-buffered saline (pH 7.4), fixed for 30 min in 4% buffered paraformaldehyde, and incubated at room temperature for 3 h with a 1:500 dilution of one of the following antibodies: monoclonal mouse anti-Olig1 (MAB2417; R&D Systems, Abingdon, UK) and anti-NG2 (MAB5384; Chemicon, Temecula, USA), polyclonal rabbit anti-Olig2 (AB9610; Chemicon, Temecula, USA). Cells were washed three times for 5 min with phosphate-buffered saline and incubated with the respective secondary antibodies (Molecular Probes, Göttingen, Germany) at a 1:500 dilution: Alexa 488 (A11055; goat anti-mouse-IgG; green fluorescence) and Alexa Fluor 546 (A11056; goat anti-rabbit-IgG; red fluorescence). The specificity of the immunoreactions was controlled by the application of buffer instead of primary antiserum.

Cell integrity analysis

Cell integrity was assessed by double labeling with propidium iodide (PI) and fluorescein diacetate [29]. The technique is based on the ability of living cells to hydrolyze fluorescein diacetate (10 µg/ml PBS, 5 min) by intracellular esterases, resulting in a green-yellow-colored fluorescence. Necrotic cells are labeled by PI (5 µg/ml

phosphate-buffered saline, 5 min), which interacts with DNA to yield a red fluorescence of cell nuclei.

Caspase 3 assay

The amino acid sequence Asp-Glu-Val-Asp (DEVD) is preferentially recognized by caspase-3 and caspase-7. DEVD-dependent protease activity was determined in culture flasks using Ac-DEVD-AFC as substrate and a commercial immunosorbent caspase 3 activity assay kit (Roche Diagnostics, Mannheim, Germany). Briefly, lysates were prepared from OLN-93 cultures, and caspase 3 was captured from the lysate in microplates coated with anti-caspase 3 monoclonal antibody. Following washing of the plates, Ac-DEVD-AFC was added and the released AFC was determined fluorometrically with 390-nm excitation and 505-nm emission filters.

Statistical analysis

Data were normally distributed (Kolmogorov–Smirnov tests). Therefore, analyses of variance (ANOVA) and post hoc *t*-tests were employed, and a probability level of $P < 0.05$ was considered to be statistically significant.

Results

Immunocytochemistry

OLN-93 cells showed positive immunolabeling for NG2, Olig1, and Olig2, markers of immature oligodendrocytes (Fig. 1).

Cell integrity analysis

Under BC, 24 h of haloperidol or clozapine treatment did not alter the percentages of propidium iodide–positive cells ($F(4,45) = 1.456$, $P = 0.231$; Fig. 2a. Twenty-four hours of SGD increased the percentages of dead OLN-93 cells in PBS-treated control cultures ($F(1,98) = 334.615$, $P < 0.001$; Fig. 2a. Haloperidol and clozapine showed partially protective effects and reduced the percentages of dead cells ($F(4,45) = 16.528$, $P < 0.001$; Fig. 2a.

Caspase 3 assay

Similarly, SGD induced a 1.6- to 1.7-fold increase in caspase 3 activity in OLN-93 cells compared with BC ($F(1,48) = 242.156$, $P < 0.001$; Fig. 2b. However, antipsychotic treatment did not modify apoptosis as measured by caspase 3 activity either under BC ($F(4,20) = 1.245$, $P = 0.324$; Fig. 2b or in response to a metabolic challenge by SGD ($F(4,20) = 0.507$, $P = 0.731$; Fig. 2b.

Discussion

It has not been fully clarified yet, whether observations of reduced OL density in postmortem studies on schizophrenia may result from disease-inherent pathomechanisms or side effects of antipsychotic treatment. Therefore, we aimed to explore the effects of haloperidol and the atypical prototype drug clozapine on the viability of immature oligodendrocytes (OLN-93 cells) under both normal (BC) and metabolic stress conditions (SGD). This novel approach has been chosen due to the current knowledge about disturbances in cerebral energy metabolism in schizophrenia. SGD led to an increased necrotic cell death rate, while treatment with haloperidol and clozapine was reducing the necrosis. In order to clarify, if this effect is also present in apoptotic cell death, the action of haloperidol and clozapine on caspase 3 activity has been assessed. Caspase 3 activity was increased in OLN-93 cells after SGD compared with the BC irrespective of antipsychotic treatment. This result shows that antipsychotic drugs are

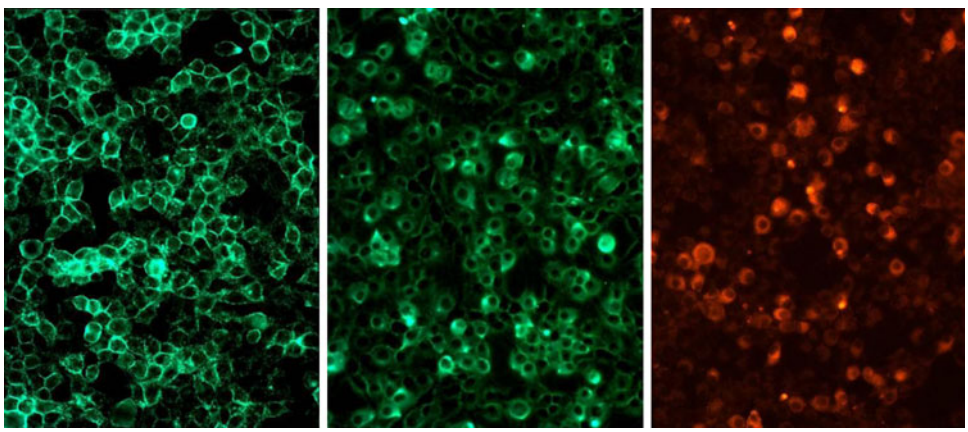

Fig. 1 Immunocytochemical characterization of OLN-93 cultures as NG2+ (*left photograph*), Olig1+ (*middle photograph*), and Olig2+ (*right photograph*) immature oligodendrocytes

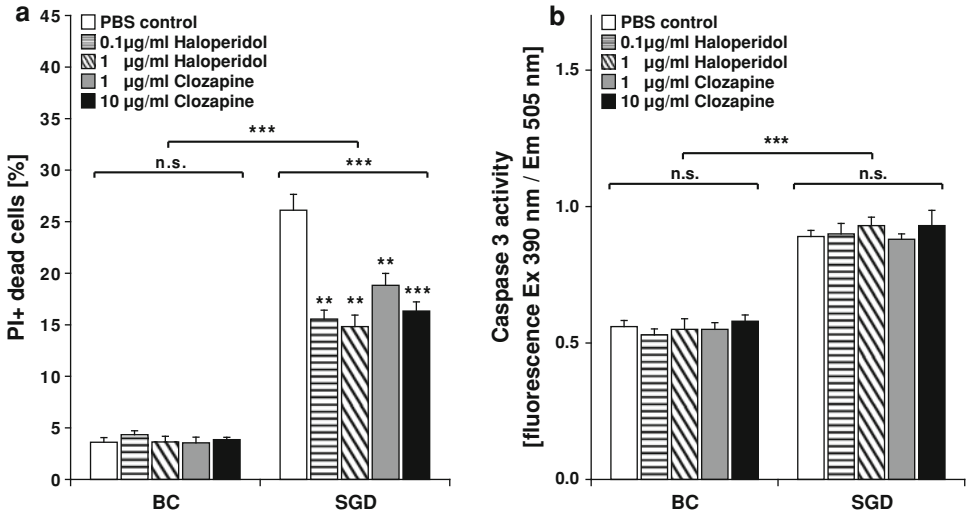

Fig. 2 **a** The percentages of necrotic dead OLN-93 cells increased significantly after SGD—with a partial protective effect of haloperidol and clozapine. **b** SGD induced a 1.6- to 1.7-fold increase in caspase 3 activity in OLN-93 cells compared with BC. However, no significant apoptosis-modulating effect of haloperidol and clozapine was observed compared with PBS-treated control cultures. *Annotation:* data are given as mean ± SEM from **a** $n = 10$ and **b** $n = 5$ cultures per treatment. Experiments were carried out twice with similar results. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, n.s. not significant

not fully but partially protective on the viability of energy-deprived OLs.

The survival-protective role of antipsychotics may be a compensatory mechanism in order to overcome altered oligodendrocyte maturation in schizophrenia by increased proliferative activity of immature OLs. This idea is in line with the studies of Niu et al. [24] and Wang et al. [35] who have shown that haloperidol is upregulating the number of NG2/Olig2 expressing OL progenitors in rodents. The OLN-93 cell line used in the present study apparently shows a similar NG2, Olig 1, and Olig 2 marker protein expression pattern (Fig. 1) and seems therefore to be a particularly suitable cell culture model for the assessment of drug effects on immature OLs. However, no such positive effects have been reported on oligodendrocyte maturation. Narayan et al. observed a downregulation of myelin/OL-related genes by haloperidol in *mouse* brain [23].

Morphometric findings in haloperidol- or olanzapine-treated macaque monkeys argue also against the assumption of detrimental drug effects, since the number of OLs was not significantly altered by treatment with these haloperidol and olanzapine for 17–27 months [16]. Quetiapine was reported to even increase the proliferation of mouse neural progenitors and to direct their differentiation to oligodendrocyte lineage, including an upregulation of myelin/OL-related genes [36] and is alleviating the cuprizone-induced white matter pathology in the brain of C57BL/6 mice [39]. These findings are in line with a longitudinal magnetic resonance diffusion tensor imaging study, which indicated that compromised myelin integrity is repaired during remission of acutely psychotic schizophrenia patients by treatment with haloperidol, risperidone, or ziprasidone [9]. Probably, these antipsychotic drugs are helpful in restoring abnormal oligodendrocyte cell cycle activity in schizophrenia [14].

Our study demonstrates that antipsychotics do not reduce OL viability in vitro (within their assumed therapeutic tissue concentration). Therefore, previously reported reductions in OL density in schizophrenia are disease related rather than a side effect of antipsychotic medication. Antipsychotics protected OLs particularly against metabolic insults by impaired energy supply, which may indicate a novel therapeutic mechanism of action. In order to get a better understanding of the influence of glucose supply on oligodendrocytes, it will be necessary to test the effects of high glucose concentrations instead of glucose deprivation in the future. This is of interest, because antipsychotic drugs are known to increase blood glucose levels [17] and to normalize the metabolic profile of cerebrospinal fluid samples from schizophrenia cases [12].

Compromised brain metabolism, oxidative stress, and OL dysfunction have been shown by gene expression and proteomic studies in schizophrenia along with impaired signaling through the insulin signaling pathway [31], low levels of IGF-1, insulin resistance, and type-2 diabetes [33]. Furthermore, insulin and IGF-1 targets AKT and GSK3 are downregulated in schizophrenia and upregulated by antipsychotics [8]. The activation of this signaling pathway is prominently involved in the regulation of energy metabolism and many aspects of oligodendroglial behavior [4]. Therefore, antipsychotics may exert their

protective effects on OLs during energy deprivation through the insulin/IGF-1/AKT pathway, which could offer new targets for future OL-directed therapy strategies in schizophrenia.

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Conflict of interest The authors declare no conflict of interest.

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