Exploring Antipsychotic-Induced Changes in Peripheral Sensory Neurons: Insights from the F11 Cell Line

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BACKGROUND

Antipsychotics are primarily used in the treatment of schizophrenia, with two main categories: typical and atypical antipsychotics. The primary difference between these groups lies in their clinical features: typical antipsychotics often produce extrapyramidal side effects such as parkinsonism, which can impact patient adherence and quality of life, while atypical antipsychotics are known to more effectively alleviate the negative symptoms of schizophrenia. Notably, some studies suggest that atypical antipsychotics may also exhibit neuroprotective effects in central nervous system neurons. Despite extensive research on their central effects, the impact of both typical and atypical antipsychotics on peripheral neurons remains poorly understood. Understanding these effects is crucial, as peripheral neurotoxicity could explain the variable outcomes observed in clinical trials assessing the impact of antipsychotics on schizophrenic patients who suffer from neuropathic pain.

To further investigate these peripheral effects, F11 cells, which are hybrids between mouse neuroblastoma cells and sensory embryonic neurons, provide a valuable model. These cells have been previously used in studies related to the pathophysiology and pharmacology of neuropathic pain, as they exhibit a high rate of proliferation but also undergo a differentiation process to acquire a neuronal phenotype. This dual capability makes them a translational model for pharmacological studies.

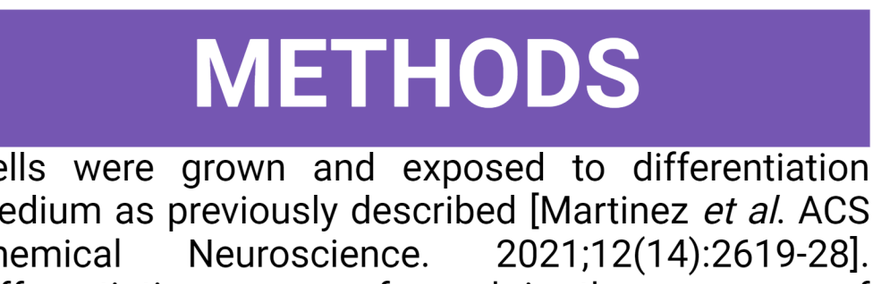
HYPOTHESIS & AIM

F11 cells could constitute a valuable model for studying the effects of typical and atypical antipsychotic drugs on sensory neurons of the peripheral nervous system

To evaluate the effect of various antipsychotics on calcium response and neurite length in differentiated F11 cells

METHODS

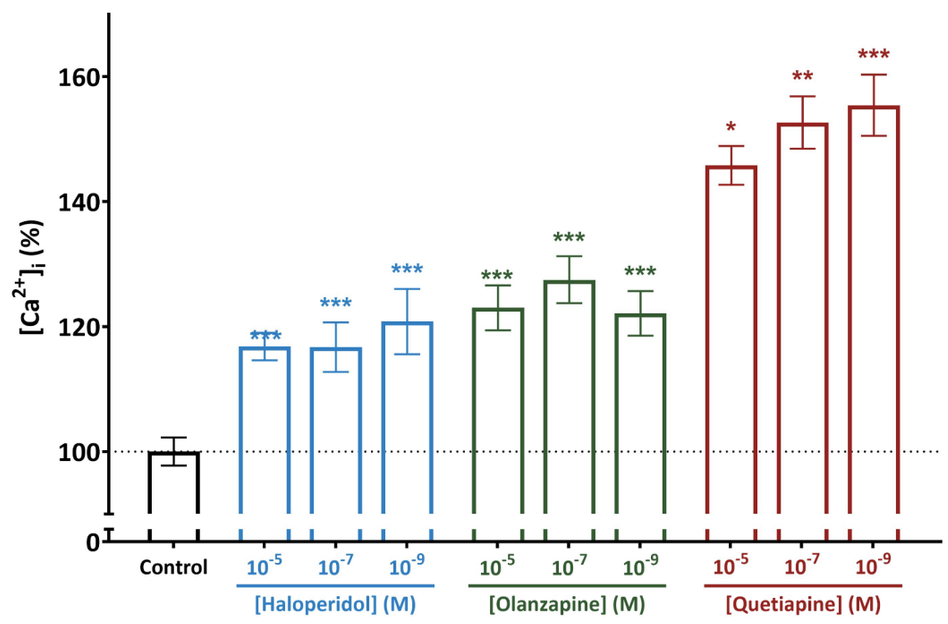
Cells were grown and exposed to differentiation medium as previously described [Martinez *et al.* ACS Chemical Neuroscience. 2021;12(14):2619-28]. Differentiation was performed in the presence of typical antipsychotic haloperidol, and atypical antipsychotics olanzapine and quetiapine in three different concentrations (10 µM, 100 nM and 1 nM). Fluorescent microscopy and excitability assays were performed as previously described (*ibidem*).



RESULTS

Exposure to both typical and atypical antipsychotics induced an increase in calcium influx in differentiated F11 cells

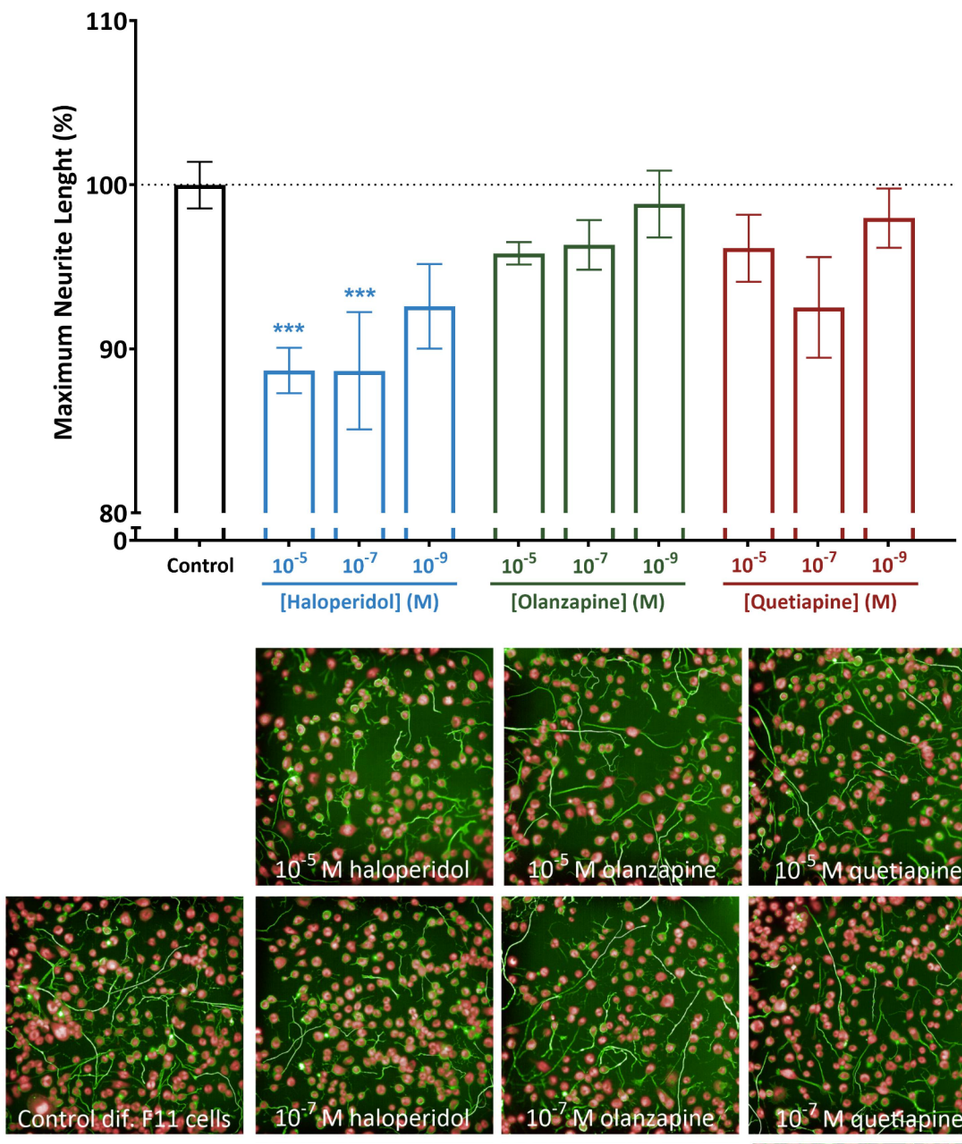
Both the typical antipsychotic haloperidol and the atypical antipsychotics olanzapine and quetiapine induced an increase in calcium influx into the cytoplasm in response to 30 mM KCl.



Changes in intracellular calcium concentration (mean ± S.E.M.) in F11 cells in response to 30 mM KCl elicited by the typical antipsychotic haloperidol and atypical antipsychotics olanzapine and quetiapine compared to control differentiated F11 cells. *p<0.05, **p<0.01, ***p<0.001, ANOVA followed by Dunnett's post hoc test.

The typical antipsychotic haloperidol induced a reduction in neurite length, whereas the atypical antipsychotics did not produce a significant reduction in differentiated F11 cells

We evaluated the effect of the exposition to the antipsychotics in neurite length observing that haloperidol elicited a dose-dependent reduction in neurite length while atypical antipsychotics olanzapine and quetiapine did not induce any significant effect on neurite outgrowth.



Changes in maximum neurite length (mean ± S.E.M.) elicited by the typical antipsychotic haloperidol and atypical antipsychotics olanzapine and quetiapine compared to control differentiated F11 cells. ***p<0.001, ANOVA followed by Dunnett's post hoc test. Representative microphotographs depict the effect of each concentration of the three compounds compared to control differentiated F11 cells.

CONCLUDING REMARKS

F11 cells constitute an effective model for evaluating the effects of antipsychotics on peripheral sensory neurons

The distinct effects observed between typical and atypical antipsychotics on the neuronal phenotype of differentiated F11 cells may provide insight into the variability in pain perception among patients undergoing antipsychotic therapy