Electrophysiological Analysis of Seroquel's Activity in Sodium Ion Channels, CiPA ion channels and hiPSC-neuronal cells

K L Rockley[1]; K Jones[1]; **M J Morton[1]**

[1]ApconiX, Alderley Park, Alderley Edge, Cheshire, UK, SK10 4TG

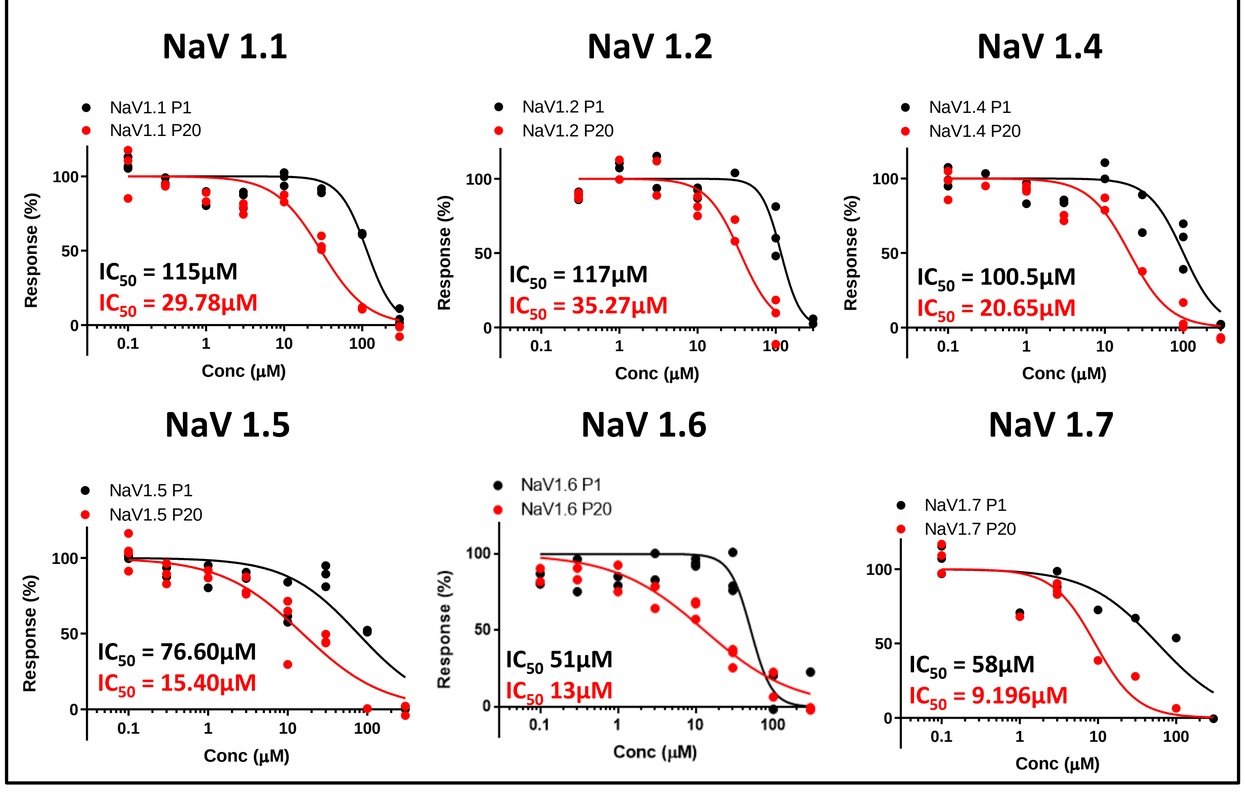
Although generally well tolerated, overdose of the antipsychotic Seroquel can cause anticholinergic syndrome, sedation/coma, seizures, tachycardia, hypotension, and prolongation of the QRS and QTc intervals. Many of these toxicities are a consequence of Seroquel's MOA (antagonism of dopamine, serotonin, adrenergic, histamine and muscarinic receptor subtypes), however prolongation of the QTc interval is due to inhibition of the herG potassium channel. Uncharacteristically this inhibition does not conclude with Torsades de Pointes, suggesting counteracting inhibition of other ion channels. To further investigate this and attain a more thorough understanding of Seroquel's activity on a range of ion channels which may contribute to the drugs toxicity profile, this work aimed to characterise the activity of Seroquel against sodium channel subtypes and the CiPA ion channel panel. In addition, the suitability of hiPSC-neuronal cells as a model to investigate the drugs neuronal effects was determined by measurement of electrical activity using microelectrode array (MEA).

METHODS

- The activity of Seroquel was tested against 6 sodium channel subtypes: **Human NaV1.1, 1.2, 1.4, 1.5, 1.6 and 1.7** and the CiPA ion channels, which were stably expressed in recombinant Chinese hamster ovary or Human embryonic kidney cell lines. Ion currents were measured by automated patch-clamp (PatchLiner, Nanion Technologies/Ion Works Quattro, Molecular devices) at ambient temperature
- IC_{50} values were estimated from 8-point concentration-response curves generated using a 3.16-fold serial dilution from top concentrations of 300µM
- Resting and use-dependence block was assessed by analysis of recorded currents at the first (P1) and final (P20) voltage steps
- hiPSC-neuronal cells (Ncardia) were cultured on 48-well MEA plates for 3 weeks before MEA analysis (Maestro Pro, Axion BioSystems). The number of active electrodes, spikes and network bursts was recorded at baseline, every hour for the following 17 hours after Seroquel addition, and following drug washout

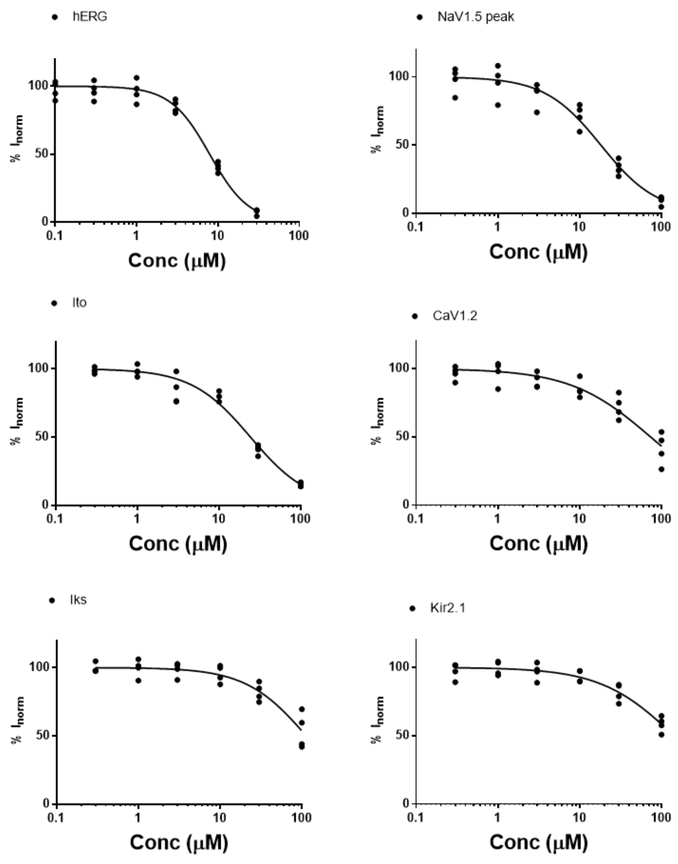
RESULTS

1. Seroquel showed similar potency and use dependence in all sodium channel subtypes tested

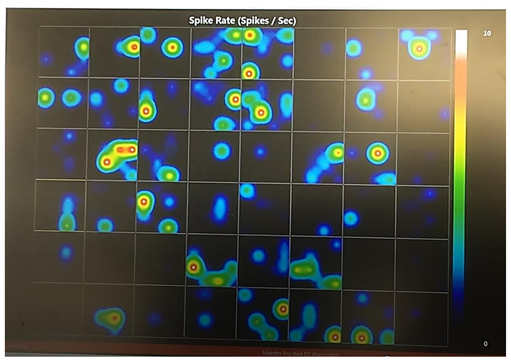


2. Seroquel CiPA

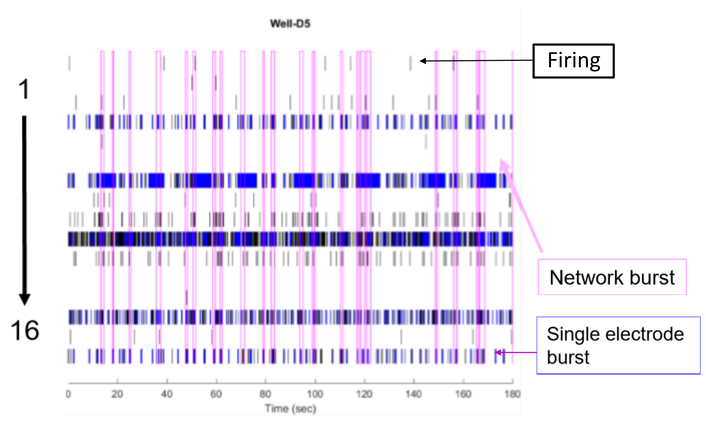
	IC_{50} µM
hERG	7.9
hNaV1.5	18.3
hKv4.3 (Ito)	24.2
hKv7.1 (Iks)	>100
hCaV1.2	73
hKir2.1	>100



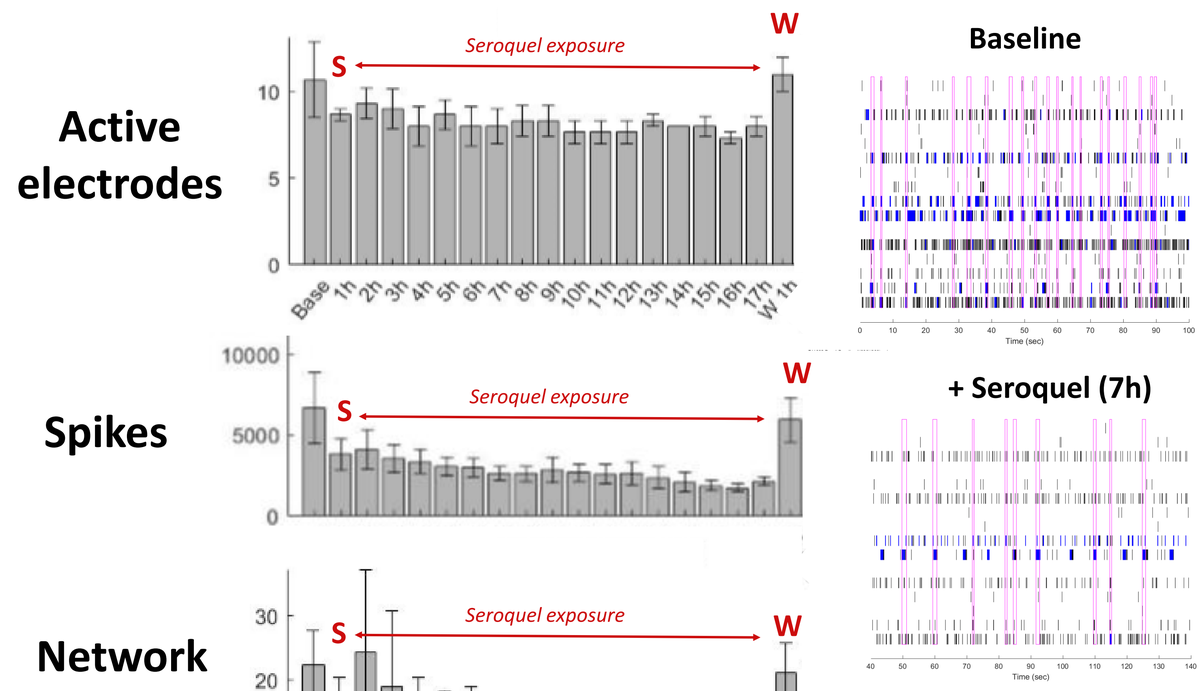
3. Seroquel (100µM) reduced neuronal firing of hiPSC-neuronal cells as measured by the number of active electrodes, spikes and network bursts in microelectrode array analysis



Heat map showing spontaneous neuronal firing of Ncardia CNS.4U hiPSC-derived neuronal cultures across a 48-well MEA plate



Raster plot showing spontaneous firing, single electrode bursts and network bursts (indicative of synchronous activity) in one well containing 16 electrodes



S = Seroquel addition
W = Drug washout

Raster plot showing reduced electrode activity, spikes and network bursts in one representative well following Seroquel addition

DISCUSSION AND CONCLUSIONS

- Due to its primarily cardiac expression, inhibition of NaV1.5 may be linked with QRS interval prolongation
- NaV1.1 and 1.2 are primarily found in the brain and linked to epilepsy, therefore inhibition may correspond to seizure risk
- Seroquel shows mixed ion channel block with greatest potency at hERG. As such it would be classified as low proarrhythmic risk.
- Following 21 days in culture hiPSC-neuronal cells showed spontaneous firing and network bursts indicative of synchronous neural activity
- The reduced electrical activity of hiPSC-neuronal cells may reflect antagonism of one or several of Seroquel's receptor targets, suggesting that these cells are a suitable model for further investigation into Seroquel's neuronal effects

Michael.morton@apconix.com