Antipsychotics and GSKIP to against neurotoxicant

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Background: GSK3 plays a crucial role in involving several physiological events at the cellular level and regulating numeral enzyme activities. It is reported to be one of the members of the AKT1/GSK3 signaling pathway, which is involved in psychopathological alterations of many psychiatric disorders. GSKIP is a naturally occurring negative regulator of GSK3, it retains both PKA RII and GSK3 binding subunit and plays a role in PKA/GSKIP/GSK3/Drp1 signaling axis. This type of autophagy event protects the cell from apoptotic damage and has been suspected that due to, in part, anti-oxidant signaling of nitro oxide.

Methods: GSKIP and antipsychotics can induce cytoprotective autophagy and protect neuronal cells from oxidative stress-induced damages. **EGFP/sh-sy5y, EGFP-GSKIP wt/sh-sy5y, EGFP-L130P/sh-sy5y, were continuously screened for more than G418, and it took more than a month until more than 80% of the cells could observe the performance of GFP, and then collected cells or successors for drug treatment or attack and acidic and autophagy inhibitor treatment experiments.**

Findings: Olanzapine, paliperidone, or haloperidol all-cause autophagic marker-LC3 performance, and three drugs treat sh-sy5y cells for 6h at 10uM, which can already be seen to stimulate the performance of p62 and LC3. Three antipsychotics, at EGFP/sh-sy5y, whether at 10uM or 50uM concentrations, processing 6h or 12h stimulates autophagic markers p62 as well as LC3 performance.

Discussions: Difference between olanzapine, sertindole, and paliperidone-induced autophagy. The different autophagy inhibitors will be applied to figure out which step of the autophagy signaling pathway is crucial. We may further identify whether GSKIP has its application in psychiatric disorders through this study. Our achievements may benefit molecular drug development in Psychopharmacology.

Table 1 Generalized estimating equation results are demonstrating the associated factors and an interaction that may affect the neuroprotective action of APDs to naïve SH-SY5Y.

Variable	β	S.E.	95% C.I.	p-value
Paliperidone vs. other drugs	4245.15	1736.26	842.15~7648.15	0.014
H_2O_2 vs. other stressors	-6051.80	1181.56	-8367.61~-3731.99	< 0.001
APD concentration	2573.80	479.84	1633.33~3514.27	< 0.001
Paliperidone*H_2O_2	5492.32	2687.82	224.29~10760.34	0.041

Dependent variable: cell number, *: interaction

Table 2 Generalized estimating equation results are showing the associated factors and possible interactions between antipsychotics and stressors in affecting neuroprotective action of APDs to naïve SH-SY5Y.

Variable	β	S.E.	95% C.I.	p-value
Hydrogen peroxide	-6143.97	1941.93	7764.38~-1647.89	< 0.001
MPP^+	991.85	2293.96	-10640.06~5875.39	0.007
APD concentration	2574.56	2491.65	-3891.70~3493.25	0.691
Paliperidone*H2O2	9680.95	468.73	1655.87~14234.05	< 0.001
Paliperidone*MPP^+	3571.84	2323.06	5127.84~9090.72	< 0.001
Paliperidone*β-amyloid	3629.23	2815.80	-1947.03~8998.30	0.205
Olanzapine*H2O2	-40.29	2739.37	-1739.84~3963.27	0.185
Olanzapine*MPP^+	2823.94	2042.67	-4043.85~7482.74	0.984
Olanzapine*β-amyloid	328.27	2376.98	-1834.87~5255.60	0.235
Risperidone*H2O2	-129.27	2513.99	-4599.05~3861.17	0.896
Risperidone*MPP^+	-3537.06	2035.98	-4119.71~491.91	0.949
Olanzapine*β-amyloid	-3505.54	2055.63	-7566.02~1358.78	0.085

Dependent variable: cell number; *interaction