

Gi	mGluR2 / 2AR	mGluR2Δ / 2AR	mGluR3 / 2AR	mGluR3Δ / 2AR
5-HT	0.43 ± 0.04	1.02 ± 0.23	0.98 ± 0.14	0.65 ± 0.26
5-HT + LY34	0.83 ± 0.18	1.07 ± 0.17	0.98 ± 0.16	1.00 ± 0.13
5-HT + LY37	0.23 ± 0.03	1.00 ± 0.05	0.87 ± 0.31	0.23 ± 0.14
LY37	0.26 ± 0.14	0.02 ± 0.01	0.021 ± 0.01	0.11 ± 0.06
Gq	mGluR2 / 2AR	mGluR2Δ / 2AR	mGluR3 / 2AR	mGluR3Δ / 2AR
Glu	1.98 ± 0.87	0.94 ± 0.27	1.07 ± 0.17	2.30 ± 0.68
Glu + Clozapine	2.80 ± 0.37	1.23 ± 0.32	0.90 ± 0.11	2.97 ± 0.29
Glu + DOI	0.99 ± 0.22	1.23 ± 0.24	1.07 ± 0.32	1.12 ± 0.37
DOI	0.35 ± 0.18	0.01 ± 0.00	0.01 ± 0.00	0.37 ± 0.16

Table S1. Cross-Signaling, DownModulation, and Upmodulation Depend on Heterocomplex Formation, Related to Figure 2

Summary of GIRK4* current activation (Gi) and IRK3 current inhibition (Gq) (mean ± SD) in oocytes expressing 2AR alone or 2AR together with mGluR2, mGluR2Δ, mGluR3, or mGluR3Δ. IRK3 current inhibition and GIRK4* current activation were measured and normalized as in Figure 1, D and E respectively. Currents were obtained in response to 1 μM of the endogenous ligand serotonin (5-HT) and 1 μM of endogenous ligand glutamate (Glu). For Gq values were obtained in response to 1 μM of the endogenous ligand serotonin (5-HT), 1 μM serotonin together with 50 μM LY34, serotonin 1 μM together with 50 μM LY37, or 50 μM LY37 alone. For Gi values were obtained in response to 1 μM of the endogenous ligand glutamate (Glu), 1 μM glutamate together with 50 μM clozapine, serotonin 1 μM together with 50 μM DOI, or 50 μM DOI alone. Gq: 5-HT, 5-HT + LY34, and 5-HT + LY37 treatments were significantly different for mGluR2/2AR and mGluR3Δ/2AR (p<0.05). Gi: Glu, Glu + Clozapine, and Glu + DOI treatments were only significantly different for mGluR2/2AR and mGluR3Δ/2AR (p<0.005).

	Δ Gi	Δ Gq	BI ₁₀	Δ Gi	Δ Gq	BI ₅₀
Clozapine	1.32	-0.98	2.3	1.68	-0.98	2.66
Risperidone	1.36	-0.82	2.18	1.69	-0.9	2.59
LY37	1.45	-0.65	2.1	1.55	-0.77	2.32
Ritanserlin	1.12	-0.77	1.89	1.17	-0.85	2.02
Methysergide	0.96	-0.80	1.76	0.95	-0.82	1.77
eGlu	0.54	-0.44	0.98	0.39	-0.45	0.84
LY34	-1.02	-0.20	-0.82	-1.07	-0.17	-0.9
DOI	-0.01	0.95	-0.96	-0.01	1.39	-1.4

Table S2. Balance Index Calculations, Related to Figure 4

Balance Index (BI) Calculations for clozapine, risperidone, LY37, methysergide, eGlu, LY34 and DOI at 10 μ M (BI₁₀) and 50 μ M concentration (BI₅₀).