Research Notes: Expression ratio-dependent $mGlu_2/5\text{-}HT_{2A}$ cross-talk

Greg Conradi Smith (w/ Javier and Spenser)

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Reproducing the observation of Moreno et al. 2016

$mGlu_{2/3}$ receptor agonist LY379268 induced increases in $[Ca^{2+}]_i$ in HEK 293 cells that co-express the $mGlu_2$ and $5\text{-}HT_{2A}$ receptors (Moreno et al., 2016). The amount of functional cross-talk (response) depends upon the ratio of expression levels of these receptors ($mGlu_2$:5-HT_{2A} of 1:1, 1:2, and 1:3). Javier mentioned that it seems counter-intuitive for the response would be a bi-phasic function of the relative expression level.

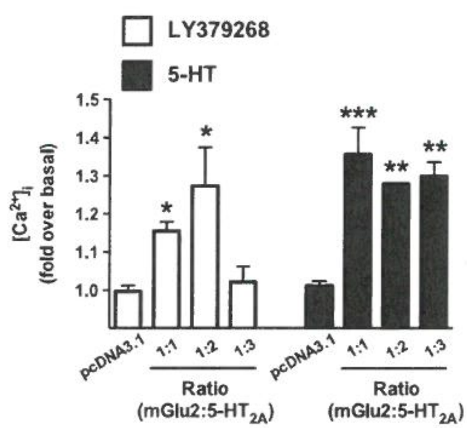

Figure 1: Panel D from Moreno et al. (2016).

Possible explanation

Greg's intuition suggested the following possible explanation. If the (cross-talk) response were (for some reason) dominated by GGH heteromers (as opposed to GGHH), then perhaps this would explain the observed dependence of response on relative expression levels. The model presented below shows that is is the case.

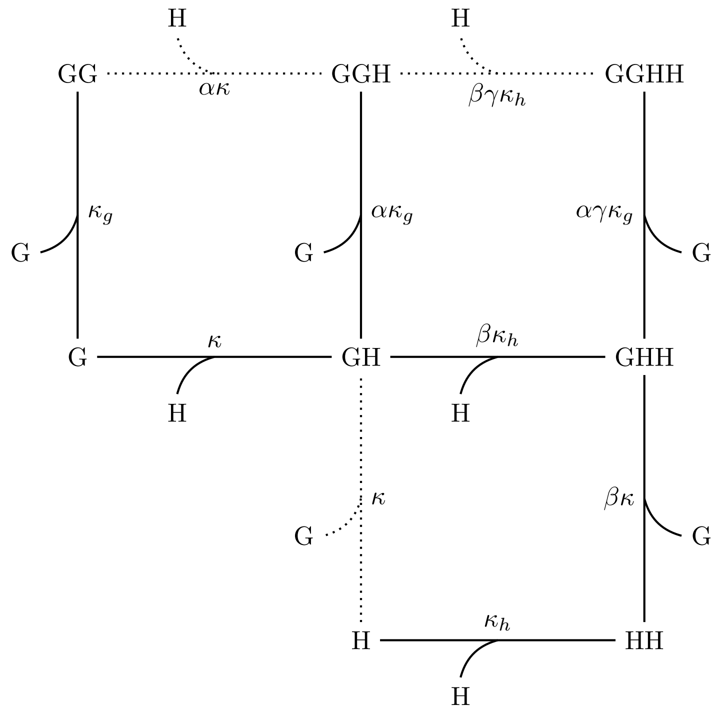

Figure 2: Diagram of bimolecular association reactions, equilibrium association costants, and allosteric parameters. Reactions used to derive Eqs. 3–8 are shown solid.

Model of dimerization and heterodimerization

Let G be the mGlu_2 monomer, H be the $5\text{-HT}_{2\mathrm{A}}$ monomer, GG and HH the homodimers, etc. The species would be G, GG, H, HH, GGH, GHH, GGHH (always writing G's before H's, order of symbols does not matter).

The total amount of G and H are given by, respectively,

$$
\begin{aligned}
G_T &= [\mathrm{G}] + 2[\mathrm{GG}] + [\mathrm{GH}] + [\mathrm{GHH}] + 2[\mathrm{GGH}] + 2[\mathrm{GGHH}] && (1) \\
H_T &= [\mathrm{H}] + 2[\mathrm{HH}] + [\mathrm{GH}] + 2[\mathrm{GHH}] + [\mathrm{GGH}] + 2[\mathrm{GGHH}]\,. && (2)
\end{aligned}
$$

The equilibrium relations are:

$$
\begin{aligned}
[\mathrm{HH}] &= \kappa_h[\mathrm{H}]^2 && (3) \\
[\mathrm{GG}] &= \kappa_g[\mathrm{G}]^2 && (4) \\
[\mathrm{GH}] &= \kappa[\mathrm{G}][\mathrm{H}] && (5) \\
[\mathrm{GGH}] &= \alpha\kappa_g[\mathrm{G}][\mathrm{GH}] = \alpha\kappa[\mathrm{GG}][\mathrm{H}] && (6) \\
[\mathrm{GHH}] &= \beta\kappa_h[\mathrm{GH}][\mathrm{H}] = \beta\kappa[\mathrm{G}][\mathrm{HH}] && (7) \\
[\mathrm{GGHH}] &= \alpha\gamma\kappa_g[\mathrm{G}][\mathrm{GHH}] = \beta\gamma\kappa_h[\mathrm{GGH}][\mathrm{H}] && (8)
\end{aligned}
$$

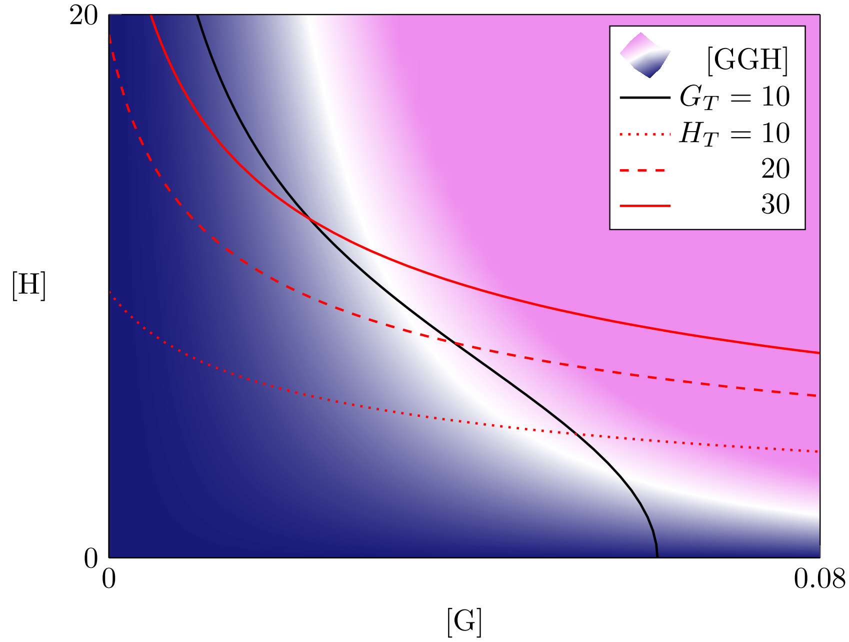

Figure 3: Contour labels are the total concentrations G_T (solid) and H_T (dashed). Increased H_T decreases [H] and increases [G]. This leads to the decreased response shown in Fig. 4.

This allows us to write Eqs. 1–2 as polynomial functions of [G] and [H]:

$$
\begin{aligned}
G_T &= [\mathrm{G}] + 2\kappa_g[\mathrm{G}]^2 + \kappa[\mathrm{G}][\mathrm{H}] && (9)\\
&+ 2\alpha\kappa_g\kappa[\mathrm{G}]^2[\mathrm{H}] + \beta\kappa_h\kappa[\mathrm{G}][\mathrm{H}]^2 + 2\alpha\beta\gamma\kappa_g\kappa_h\kappa[\mathrm{G}]^2[\mathrm{H}]^2 && (10)\\
H_T &= [\mathrm{H}] + 2\kappa_h[\mathrm{H}]^2 + \kappa[\mathrm{G}][\mathrm{H}] && (11)\\
&+ \alpha\kappa_g\kappa[\mathrm{G}]^2[\mathrm{H}] + 2\beta\kappa_h\kappa[\mathrm{G}][\mathrm{H}]^2 + 2\alpha\beta\gamma\kappa_g\kappa_h\kappa[\mathrm{G}]^2[\mathrm{H}]^2 && (12)
\end{aligned}
$$

Define $f_G([\mathrm{G}],[\mathrm{H}]) := G_T - ([\mathrm{G}] + 2\kappa[\mathrm{G}]^2 + \cdots + 2\alpha\beta\gamma\kappa_g\kappa_h\kappa[\mathrm{G}]^2[\mathrm{H}]^2)$ and similarly for $f_H([\mathrm{G}],[\mathrm{H}])$, and notice that f_G and f_H are both increasing functions of [G] and [H]. For this reason is straightforward to numerically calculate the equilibrium concentrations of G and H. The answer depends on the chosen parameters: two expression levels, i.e., the total concentrations G_T and H_T, three equilibrium association constants (κ_g, κ_h, κ), and three allosteric parameters (α, β, γ).

Fig. 3 shows how these equilibrium concentrations of [G] and [H] are given by the intersection of the curves $f_G([\mathrm{G}],[\mathrm{H}];G_T) = 0$ and $f_H([\mathrm{G}],[\mathrm{H}];H_T) = 0$, the locations of which depend on G_T and H_T, respectively.

In Fig. 3, three increasing values of H_T are used (G_T is fixed). The curve intersections show [G] decreasing and [H] increasing as the $G_T : H_T$ expression ratio changes from 1:1 to 1:2 to 1:3. Assuming that the functional cross-talk is proportional to [GGH], this results in a decreasing response (see Fig. 4), reproducing the counterintuitive experimental observation of Moreno et al. (2016) shown in Fig. 1.

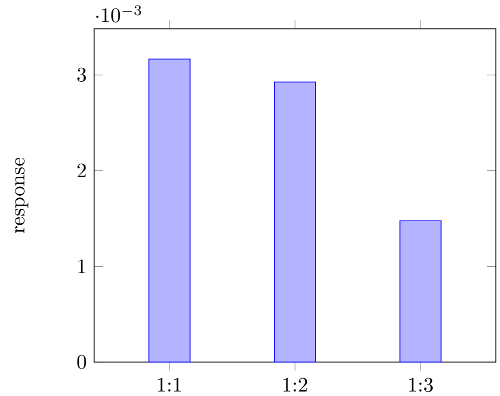

Figure 4: Response for three different values of $G_T : H_T$. Parameters: $\kappa = 0.25$, $\kappa_g = 1300$, $\kappa_h = 0.001$, $\alpha = 0.001$, $\beta = 10000$, $\gamma = 0.001$. The response is assumed to be proportional to [GGH].

For discussion

- Many parameter sets do not lead to the counter-intuitive response. What is it about these parameter values that leads to the counter-intuitive response?
- Is there any biological reason to think that the amount of functional cross-talk might be greater in GGH than GGHH? (This is the primary assumption that makes the model reproduce the counter-intuitive response, so perhaps we should discuss whether or not this assumption could be biologically realistic.)

References

José L Moreno, Patricia Miranda-Azpiazu, Aintzane Garcia-Bea, Jason Younkin, Meng Cui, Alexey Kozlenkov, Ariel Ben-Ezra, Georgios Voloudakis, Amanda K Fakira, Lia Baki, Yongchao Ge, Anastasios Georgakopoulos, José A Morón, Graeme Milligan, Juan F López-Giménez, Nikolaos K Robakis, Diomedes E Logothetis, J Javier Meana, and Javier González-Maeso. Allosteric signaling through an mGlu2 and 5-HT2A heteromeric receptor complex and its potential contribution to schizophrenia. *Science Signaling*, 9(410): ra5–ra5, 2016.