Supplemental information

Antidepressant drugs act by directly binding
to TRKB neurotrophin receptors

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Table S1. Simulated systems discussed in this study. The table lists the variant of TRKB dimers, mole percentage of cholesterol ($\rho_{\text{CHOL}}$), the number of POPC ($N_{\text{POPC}}$), cholesterol ($N_{\text{CHOL}}$), and drug ($N_{\text{DRUG}}$) molecules, temperature ($T$), the number of simulation repeats ($N_{\text{sim}}$), and the simulation length per repeat ($t_{\text{sim}}$). “WT,” “Y433F.het”, “V437A.hom”, “S440A.hom” refer in respective order to the wild-type, heterozygous Y433F, homozygous V437A, and homozygous S440A variants of TRKB TM dimer (residues 427-459) and TRKA TM dimer (residues 410-443). FLX: fluoxetine, SKE: S-ketamine “Protein-free” refers to the systems without the protein in the membrane. Related to Fig. 1G-J and Fig. 3.

| System name | Protein variant | Drug type | $\rho_{\text{CHOL}}$ (mol%) | $N_{\text{POPC}}$ | $N_{\text{CHOL}}$ | $N_{\text{DRUG}}$ | $T$ (K) | $N_{\text{sim}}$ | $t_{\text{sim}}$ (µs) |
|-------------|----------------|-----------|----------------------------|-----------------|----------------|----------------|--------|---------------|----------------|
| System 1$^1$ | WT TRKB | 0 | 128 | 0 | 363 | 10 | 1 |
| System 2$^1$ | WT TRKB | 20 | 90 | 28 | 363 | 10 | 1 |
| System 3$^1$ | WT TRKB | 40 | 90 | 60 | 363 | 10 | 1 |
| System 4$^1$ | Y433F.het TRKB | 20 | 112 | 28 | 363 | 10 | 1 |
| System 5 | WT TRKB | 0 | 128 | 0 | 310 | 10 | 1 |
| System 6 | WT TRKB | 20 | 112 | 28 | 310 | 10 | 1 |
| System 7 | WT TRKB | 40 | 90 | 60 | 310 | 10 | 1 |
| System 8 | Y433F.het TRKB | 20 | 112 | 28 | 310 | 10 | 1 |
| System 9 | WT TRKB | 20 | 112 | 28 | 310 | 10 | 1 |
| System 10 | WT TRKB | 20 | 112 | 28 | 310 | 10 | 1 |
| System 11 | WT TRKB | 20 | 112 | 28 | 310 | 10 | 1 |
| System 12 | Y433F.het TRKB | 20 | 112 | 28 | 310 | 10 | 1 |
| System 13 | V437A.hom TRKB | 20 | 112 | 28 | 310 | 10 | 1 |
| System 14 | S440A.hom TRKB | 20 | 112 | 28 | 310 | 10 | 1 |
| System 15$^1$ | WT TRKA | 0 | 128 | 0 | 363 | 10 | 1 |
| System 16$^1$ | WT TRKA | 20 | 90 | 60 | 310 | 10 | 1 |
| System 17$^1$ | WT TRKA | 40 | 90 | 60 | 310 | 10 | 1 |
| System 18 | WT TRKA | 0 | 128 | 0 | 310 | 10 | 1 |
| System 19 | WT TRKA | 20 | 112 | 28 | 310 | 10 | 1 |
| System 20 | WT TRKA | 40 | 90 | 60 | 310 | 10 | 1 |
| System 21 | protein-free | 0 | 200 | 0 | 310 | 1 | 0.5 |
| System 22 | protein-free | 20 | 160 | 40 | 310 | 1 | 0.5 |
| System 23 | protein-free | 40 | 120 | 80 | 310 | 1 | 0.5 |
| System 24 | protein-free | 0 | 200 | 0 | 10 | 310 | 1 | 0.5 |
| System 25 | protein-free | 20 | 160 | 40 | 310 | 1 | 0.5 |
| System 26 | protein-free | 40 | 120 | 80 | 310 | 1 | 0.5 |
| System 27 | protein-free | 0 | 200 | 0 | 20 | 310 | 1 | 0.5 |
| System 28 | protein-free | 20 | 160 | 40 | 310 | 1 | 0.5 |
| System 29 | protein-free | 40 | 120 | 80 | 310 | 1 | 0.5 |
| System 30 | protein-free | 0 | 200 | 0 | 40 | 310 | 1 | 0.5 |
| System 31 | protein-free | 20 | 160 | 40 | 310 | 1 | 0.5 |
| System 32 | protein-free | 40 | 120 | 80 | 310 | 1 | 0.5 |
| System 33 | protein-free | 0 | 200 | 0 | 10 | 310 | 1 | 0.5 |
| System 34 | protein-free | 20 | 160 | 40 | 310 | 1 | 0.5 |
| System 35 | protein-free | 40 | 120 | 80 | 310 | 1 | 0.5 |
| System 36 | protein-free | 0 | 200 | 0 | 20 | 310 | 1 | 0.5 |
| System 37 | protein-free | 20 | 160 | 40 | 310 | 1 | 0.5 |
| System 38 | protein-free | 40 | 120 | 80 | 310 | 1 | 0.5 |
| System 39 | protein-free | 0 | 200 | 0 | 40 | 310 | 1 | 0.5 |
| System 40 | protein-free | 20 | 160 | 40 | 310 | 1 | 0.5 |
| System 41 | protein-free | 40 | 120 | 80 | 310 | 1 | 0.5 |
† These simulations were performed in the NVT ensemble, after initial equilibration at 310 K to achieve the correct area per lipid. A flat-bottomed half-harmonic restraint (force constant of 1000 kJ/mol/nm²) was used for TRKB systems to keep the inter-helical distance between the Gly443 Ca atoms below 0.45 nm during the simulations to prevent dissociation of the helices and to achieve proper local sampling (see details above). All other simulations were performed in the NpT ensemble.