**Supplemental Materials for:**

**Effects of repeated kappa-opioid receptor agonist U-50488 treatment and subsequent termination**

**on intracranial self-stimulation in male and female rats**

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**Table 1:** Group mean EF0 values (95% confidence limits) in female rats (n=5), male rats (n=6), and combined sexes (n=11) for baseline and following repeated 3.2 mg/kg/day or 5.6 mg/kg/day U-50488. There was no significant main effect of sex, nor a significant sex × day interaction. Therefore, males and females were combined, and a one-way repeated measures ANOVA was performed. \* denotes significantly (p<0.05) different from baseline EF0 value based on results from one-way repeated measures ANOVA (F3.66,36.61=7.81, p=0.002) and a Sidak post-hoc test.

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| **Experimental Condition** | **Females EF0**  **(95% CL)** | **Males EF0**  **(95% CL)** | **Group EF0**  **(95% CL)** |
| ***3.2 mg/kg U-50488*** |  |  |  |
| Average Baselines | 78.3 (70.8, 86.7) | 70.9 (62.9, 80) | 74.2 (72.5, 75.9) |
| Day 1 | 84 (78.6, 89.8) | 77.3 (66.7, 89.6) | 80.3 (73.7, 87.5) |
| Day 2 | 81.2 (71.4, 92.4) | 81.9 (73.4, 91.4) | 81.6 (75.3, 88.3) |
| Day 3 | 82.8 (75.8, 90.4) | 71.9 (62.6, 82.6) | 76.7 (69.9, 84.1) |
| Day 4 | 79.8 (75.8, 84) | 84.2 (74.1, 95.7) | 82.2 (76.5, 88.4) |
| Day 5 | 81.1 (70.1, 93.9) | 76.5 (67.8, 86.3) | 78.6 (71.8, 86) |
| Day 6 | 82.5 (72.3, 94.3) | 79 (68.4, 91.3) | 80.6 (73.3, 88.7) |
| ***5.6 mg/kg U-50488*** |  |  |  |
| Average Baselines | 76 (66.4, 87) | 71.7 (64.9, 79.3) | 73.7 (72.4, 74.9) |
| Day 1 | 95.7 (85.5, 107.1) | 96.3 (88, 105.3) | 96 (89.8, 102.7) \* |
| Day 2 | 86 (70.8, 104.4) | 102.5 (95.3, 110.3) | 94.6 (85.1, 105.2) \* |
| Day 3 | 88.8 (79.4, 99.2) | 89.6 (79.7, 100.7) | 89.2 (82.6, 96.4) \* |
| Day 4 | 89.2 (84.6, 94.6) | 83 (71.9, 96) | 85.8 (79, 93.2) \* |
| Day 5 | 89.3 (81.9, 97.3) | 90.8 (83.6, 98.6) | 90.1 (85.1, 95.4) \* |
| Day 6 | 86 (75.6, 97.8) | 93 (88.6, 97.5) | 89.7 (84.1, 95.7) \* |

**Table 2:** Group mean EF0 values (95% confidence limits) in female rats (n=5), male rats (n=6), and combined sexes (n=11) for baseline and following repeated 3.2 mg/kg/day or 5.6 mg/kg/day U-50488. There was no significant main effect of sex, nor a significant sex × day interaction. Therefore, males and females were combined for statistical analyses. Within a given experimental type (i.e. baseline, 1 mg/kg U-50488, etc.), there was no significant main effect of test session.

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| **Experimental Condition** | **Females EF0**  **(95% CL)** | **Males EF0**  **(95% CL)** | **Group EF0**  **(95% CL)** |
| ***Sequential Test #1*** | | | |
| Baseline | 73.3 (62.7, 85.8) | 75.7 (68.8, 83.2) | 74.6 (68.6, 81.1) |
| 1 mg/kg U-50488 | 77 (67.2, 88.3) | 73.4 (67.2, 80.1) | 75.0 (69.6, 80.9) |
| 3.2 mg/kg U-50488 | 94.9 (87.1, 103.5) | 93.9 (80.2, 109.9) | 94.4 (86.2, 103.3) |
| 5.6 mg/kg U-50488 | 108.7 (100.1, 118) | 108.9 (101.9, 116.5) | 108.8 (103.6, 114.4) |
| ***Sequential Test #2 (Post-repeated saline)*** | | | |
| Baseline | 73.9 (64.7, 84.5) | 75.3 (67.3, 84.3) | 74.7 (68.8, 81.1) |
| 1 mg/kg U-50488 | 74.3 (67.4, 81.8) | 73.5 (65, 83.2) | 73.9 (68.4, 79.7) |
| 3.2 mg/kg U-50488 | 88 (83.4, 92.8) | 94.3 (80.7, 110) | 91.4 (83.8, 99.6) |
| 5.6 mg/kg U-50488 | 106 (83.9, 134) | 104.5 (92.1, 118.5) | 105.2 (93.3, 118.6) |
| ***Sequential Test #3 (Post-repeated 3.2 mg/kg/day U-50488)*** | | | |
| Baseline | 75.5 (68.2, 83.6) | 71 (62.9, 80.1) | 73.0 (67.5, 79) |
| 1 mg/kg U-50488 | 80.6 (75.8, 85.8) | 70.1 (60.2, 81.7) | 74.7 (68, 82.1) |
| 3.2 mg/kg U-50488 | 85.6 (75.2, 97.5) | 87.4 (80, 95.3) | 86.6 (80.6, 93.0) |
| 5.6 mg/kg U-50488 | 111.3 (101.4, 122.2) | 116.2 (104, 129.7) | 113.9 (106.1, 122.3) |
| ***Sequential Test #4 (Post-repeated 5.6 mg/kg/day U-50488)*** | | | |
| Baseline | 61.0 (59.1, 63) | 68.2 (63.7, 73.2) | 64.9 (61.6, 68.3) |
| 1 mg/kg U-50488 | 62.2 (57.7, 67.1) | 71.1 (64.4, 78.4) | 66.9 (62.2, 72) |
| 3.2 mg/kg U-50488 | 90.3 (83.1, 98.2) | 78.8 (70.3, 88.3) | 83.8 (77.3, 90.9) |
| 5.6 mg/kg U-50488 | 105.5 (94.8, 117.4) | 97.6 (90.8, 104.9) | 101.1 (94.9, 107.8) |
| ***Sequential Test #5 (7-day post-repeated 5.6 mg/kg/day U-50488)*** | | | |
| Baseline | 74.5 (63.4, 87.5) | 72.7 (64.7, 81.6) | 73.5 (67.1, 80.6) |
| 1 mg/kg U-50488 | 78 (70.3, 86.6) | 70.5 (59.4, 83.5) | 73.8 (66.5, 81.9) |
| 3.2 mg/kg U-50488 | 80.6 (65.9, 98.5) | 82.5 (74.5, 91.3) | 81.6 (73.8, 90.3) |
| 5.6 mg/kg U-50488 | 111 (96.4, 127.9) | 107.8 (97.2, 119.6) | 109.3 (100.7, 118.5) |
| ***Sequential Test #6 (28-day post-repeated 5.6 mg/kg/day U-50488)*** | | | |
| Baseline | 75.5 (66.3, 86.1) | 76.8 (69.3, 85.1) | 76.2 (70.6, 82.4) |
| 1 mg/kg U-50488 | 76 (65.1, 88.7) | 80.3 (75.1, 85.9) | 78.3 (72.5, 84.6) |
| 3.2 mg/kg U-50488 | 89 (72.4, 109.4) | 84.6 (69.9, 102.4) | 86.6 (75.8, 99) |
| 5.6 mg/kg U-50488 | 105.7 (82.1, 136.2) | 107.1 (97.3, 117.8) | 106.5 (94.5, 119.9) |