

## Ion Channels

| Gene Knockout/Overexpression*                                                         | Background                                                                         | Operant | 2BC                                                                          | CIE            | DID                                                                         | References                     |
|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------|------------------------------------------------------------------------------|----------------|-----------------------------------------------------------------------------|--------------------------------|
| Transient receptor potential cation channel, subfamily M member 5 ( <i>Trpm5</i> )    | B6                                                                                 |         | ↓                                                                            |                |                                                                             | Blednov et al., 2008 [162]     |
|                                                                                       | B6 × 129X1/SvJ                                                                     |         | ↑                                                                            |                |                                                                             | Blednov and Harris, 2009 [183] |
| Transient receptor potential cation channel, subfamily V member 1 ( <i>Trpv1</i> )    |                                                                                    |         |                                                                              |                |                                                                             |                                |
| Galanin-3 receptor ( <i>Galr3</i> )                                                   | B6                                                                                 | ↑       | ↑                                                                            |                |                                                                             | Genders et al., 2018 [372]     |
| G protein-activated inward rectifier potassium channel 2, GIRK2 ( <i>Kcnj6</i> )      | B6 × 129Sv                                                                         |         | — bottle alternation; males/females<br>↑ without bottle alternation; females |                |                                                                             | Blednov et al., 2001 [30]      |
| G protein-activated inward rectifier potassium channel 3, GIRK3 ( <i>Kcnj9</i> )      | B6                                                                                 |         | ↑ (2 h)                                                                      |                |                                                                             | Herman et al., 2015 [309]      |
|                                                                                       | B6                                                                                 |         | —<br>↑ (20%)<br>— (3%, 6%, 10%)                                              |                |                                                                             | Kozell et al., 2018 [          |
| G protein-coupled receptor GPR88 ( <i>Gpr88</i> )                                     | C57B1/6 (13/96%), C57B1/6J (60.94%), FVB/N (0.05%), 129/SvPas (25%), SJL/J (0.05%) | ↑       | ↑ (10%)<br>↑ (20% intermittent))                                             |                |                                                                             | Ben Hamida et al., 2018 [371]  |
| β-arrestin-1 ( <i>Arrb1</i> )                                                         | B6                                                                                 |         | —                                                                            |                |                                                                             | Bjork et al., 2008 [168]       |
|                                                                                       | B6                                                                                 |         |                                                                              |                | ↑ females vs. Het females (10%, 4 h)<br>↑ females vs. Het and WT (20%, 4 h) | Robins et al., 2018            |
| β-arrestin-2 ( <i>Arrb2</i> )                                                         | B6                                                                                 |         | ↓ 9-15%                                                                      |                |                                                                             | Bjork et al., 2008 [168]       |
|                                                                                       | B6                                                                                 |         | ↑                                                                            |                |                                                                             | Li et al., 2013 [283]          |
|                                                                                       | B6                                                                                 |         |                                                                              |                | — (10%, 4 h)                                                                | Chiang et al., 2016            |
|                                                                                       | B6                                                                                 |         |                                                                              |                | ↑ (10%, 4 h)                                                                | Robins et al., 2018 [373]      |
| Voltage-dependent N-type calcium channel subunit α-1B ( <i>Cacna1b</i> )              | B6 × 129SvJae                                                                      |         | ↓                                                                            |                |                                                                             | Newton et al., 2004 [94]       |
| EF hand domain containing 2 (aka, swiprosin-1; <i>Efh2</i> ; calcium-sensing protein) | B6                                                                                 |         | ↑                                                                            |                |                                                                             | Mielenz et al., 2018 [374]     |
| Calcium-activated potassium channel subunit β-1, BK β1 ( <i>Kcnmb1</i> )              | B6                                                                                 |         | —<br>— intermittent                                                          | ↑ <sup>a</sup> | — (2 h)                                                                     | Kreifeldt et al., 2013 [290]   |
| Calcium-activated potassium channel subunit β-4, BK β4 ( <i>Kcnmb4</i> )              | B6                                                                                 |         | — continuous<br>— intermittent                                               | ↓ <sup>a</sup> | — (2 h)                                                                     | Kreifeldt et al., 2013 [290]   |
|                                                                                       | B6                                                                                 |         |                                                                              |                | ↑ (2 h; males/females)                                                      | Martin et al., 2008 [179]      |

|                                                                               |                       |                                |                                                                                                                |                                  |
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| P2X purinoceptor 4 ( <i>P2rx4</i> )                                           | B6                    | ↑ intake                       | ↑ transient (4 h; 5%, 20%)<br>— (4 h, 10%)                                                                     | Wyatt et al., 2014 [292]         |
| Glycine receptor subunit $\alpha 2$ ( <i>Glr2</i> )                           | B6                    | ↑                              |                                                                                                                | Khoja et al., 2018 [364]         |
|                                                                               | B6                    | ↓ continuous<br>— intermittent | — (2, 4 h, 1B)                                                                                                 | Blednov et al., 2015 [324]       |
|                                                                               | B6                    |                                | ↑ (15%, 2 h, 4 h, males, days 1 and 2)<br>— (15%, 2 h, 4 h, males, days 3 and 4)<br>— (15%, 2 h, 4 h, females) | San Martin et al., 2020 [384]    |
| Glycine receptor subunit $\alpha 3$ ( <i>Glr3</i> )                           | B6                    | — continuous<br>↑ intermittent | — (2 h, 4 h, 1B)                                                                                               | Blednov et al., 2015 [324]       |
| Nicotinic acetylcholine receptor (nAChR) $\alpha 4$ subunit ( <i>Chrna4</i> ) | B6                    |                                | ↓ (2 h, 20%)<br>— (2 h, 2%)                                                                                    | Hendrickson et al., 2010 [209]   |
| nAChR $\alpha 5$ subunit ( <i>Chrna5</i> )                                    | B6                    |                                | — (4 h)                                                                                                        | Santos et al., 2013 [286]        |
| nAChR $\alpha 6$ subunit ( <i>Chrna6</i> )                                    | B6                    | — males/females                |                                                                                                                | Kamens et al., 2012 [263]        |
|                                                                               | C57BL/6J              |                                | — males/females (2-20%)                                                                                        | Guildford et al., 2016 [325]     |
| nAChR $\alpha 7$ subunit ( <i>Chrna7</i> )                                    | B6                    | ↓ females<br>— males           |                                                                                                                | Kamens et al., 2010 [229]        |
| nAChR $\beta 2$ subunit ( <i>Chrb2</i> )                                      | B6                    | — males/females                |                                                                                                                | Kamens et al., 2010 [229]        |
|                                                                               | B6                    | — intermittent                 |                                                                                                                | Dawson et al., 2013 [276]        |
| nAChR $\beta 3$ subunit ( <i>Chrb3</i> )                                      | B6                    | — males/females                |                                                                                                                | Kamens et al., 2012 [263]        |
| nAChR $\beta 4$ subunit ( <i>Chrb4</i> )                                      | C57BL/6J              |                                | — males (2 h, 20%)                                                                                             | Patkar et al., 2016 [332]        |
|                                                                               | B6                    | — females (24 h)               | — males/females (4 h)                                                                                          | Kamens et al., 2017 [355]        |
| nAChR $\alpha 5\alpha 3\beta 4^*$                                             | B6SJLF1/J             | ↓ intake                       |                                                                                                                | Gallego et al., 2012 [262]       |
| Sodium bicarbonate transporter NBCn1 ( <i>Slc4a7</i> )                        | C57BL/6J              | ↑ males                        |                                                                                                                | Schank et al., 2020 (376)        |
| Hyperpolarization-activated cyclic nucleotide-gated channel 1 ( <i>Hcn1</i> ) | B6 $\times$ 129s/SvEv | ↑                              |                                                                                                                | Salling and Harrison, 2020 [383] |

—, ↓, ↑: no difference, decreased ethanol intake and/or preference, or increased ethanol intake and/or preference, respectively, in knockout vs. wildtype mice. Male mice were tested unless otherwise indicated. Ethanol intake in the two-bottle (2BC) test was measured in 24-h sessions unless otherwise indicated. Drinking session times for the other tests are indicated in parenthesis. CIE, chronic intermittent ethanol; DID, drinking in the dark; 1B, one bottle. <sup>a</sup> These tests involved weekly limited access (2 h/day) 2BC drinking alternated with weekly CIE vapor (16 h/day) to create alcohol dependence/withdrawal. Deletion of BK  $\beta 4$  attenuated, while deletion of BK  $\beta 1$  accelerated, the escalation of ethanol drinking in dependent mice during withdrawal from CIE. Recommended mouse protein and gene (in italics) names are from Uniprot. B6 refers to C57BL/6J mice.