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Short communication

# Sigma-1 receptor knockout mice display a depressive-like phenotype

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ABSTRACT

Activation of sigma-1 receptors (Sig-1R) reportedly has antidepressant-like action. Limited data suggest that Sig-1Rs also modulate anxiety-related behaviors. The present experiments measured depressive-like, anxiety-like and motor behavior in Sig-1R knockout mice and their wildtype littermates. Sig-1R knockout mutants showed increased immobility in the forced swimming test, a depressive-like phenotype, but normal anxiety-like behavior in the elevated plus-maze and light/dark box tests and normal locomotor activity. The results further suggest that Sig-1Rs inversely modulate depressive-like behavior.



Sigma receptors (SigRs) are non-opioid, non-phencyclidine, intracellular receptors that modulate multiple signal transduction and neurotransmitter systems. Two different SigR subtypes are known, Sig-1R and Sig-2R, which differ in their binding profile and molecular weight [17,20,34]. The Sig-1R gene [33,37,44] encodes a 29 kDa polypeptide containing one or two putative transmembrane domains. Sig-1Rs are widely expressed in rat brain, especially within limbic systems and brainstem motor structures. The highest levels of Sig-1R immunostaining are observed in the olfactory bulb, hypothalamus and hippocampus, with the caudate-putamen, septum, nucleus accumbens and amygdala also showing moderately concentrated, intense labeling [2,6,38]. In animal models, blockade of Sig-1Rs is known to attenuate the rewarding and toxic properties of drugs of abuse, including psychostimulants and ethanol [18,28,32,42]. Conversely, activation of Sig-1R exerts neuroprotective effects and attenuates learning and memory impairments [11,30,31].

More recently, Sig-1R systems have also been studied for their possible relation to depressive- or anxiety-related behavior. Mounting pharmacological data suggest an antidepressant-like action of selective Sig-1R agonists. Chemically unrelated Sig-1R agonists, such as (+)-pentazocine, 1,3-di-o-tolyguanidine (DTG), SA-4503, igmesine and additional novel ligands, dose-dependently reduce immobility in animal models of behavioral despair, including the forced swim and/or tail suspension tests; the antidepressant-like action induced by these ligands is reversed by the selective Sig-1R antagonist NE-100 [1,29,46,49]. Moreover, antidepressant-like actions of the neurosteroids dehydroepiandrosterone sulfate and pregnenolone, putative endogenous ligands for Sig-1Rs, also appear to be mediated, at least partly, by Sig-1Rs [15,41,47]. Finally, many structurally distinct psychotropic drugs used clinically as antidepressants bind Sig-1Rs with high affinity [23,35,43,50]; in animal models, antidepressant-like actions of several such compounds, including fluovoxamine, venlafaxine and bupropion, can be abolished by pretreatment with a Sig-1R antagonist [14,16,49].

The few studies that have investigated the role of Sig-1Rs in anxiety-related behavior have obtained conflicting results. The SigR agonists (+)-SKF-10,047 and dextromethorphan, but not (+)-pentazocine or DTG, ameliorated conditioned fear stress [24,36]. A patent application asserted that disubstituted guanidines with high affinity for SigRs exert anxiolytic-like activity (International Application No. PCT/US1990/002398, 02.05.1990), a claim not yet peer-reviewed.

Recently, separate lines of Sig-1R knockout (Sig-1R KO) mice were generated by gene targeting ($Oprs1^{tm1Lmon}$/$Oprs1^{tm1Lmon}$) [26] and gene trapping ($Oprs1^{Gt(IRESBetageo)33Lex}$/$Oprs1^{Gt(IRESBetageo)33Lex}$) methods. Both knockout models were viable and fertile with negligible overt phenotype observed in cursory observations using limited sample sizes; the former model showed only a blunted hypomotility response to the SigR agonist (+)-SKF-10,047 [7,26] (http://www.informatics.jax.org/external/

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ko/lexicon/2691.html). Because of the pharmacological evidence suggesting a role of Sig-1Rs in depressive- or anxiety-like behaviors, the present study tested large samples of $Oprs1^{Gt(IRESBetageo)33Lex}$/$Oprs1^{Gt(IRESBetageo)33Lex}$ null mutant and wildtype littermate mice in selected tests of depression- and anxiety-related behaviors.

Heterozygote Oprs1 mutant (+/−) $Oprs1^{Gt(IRESBetageo)33Lex}$ embryos on a C57BL/6J × 129S/SvEv mixed background were obtained from the Mutant Mouse Resource Regional Center (MMRRC) and implanted into female C57BL/6J mice (Jackson Laboratories, Bar Harbor, ME) at The Scripps Research Institute. The first generation yielded wildtype (+/+, WT) and heterozygous mice (+/−) which were then subjected to heterozygous mating. The resulting male, adult null mutant mice (Oprs1 −/−, Sig-1R KO) and their age-matched, WT littermates were subjects in this study. PCR was used to assess the presence vs. absence of the native Oprs1 transcript [primer sequences: (a) 5′-TCTGAGTACGTGCTGCTCTTCG-3′, (b) 5′-ATAAACCCTCTTGCAGTTGCATC-3′, (c) 5′-GAAACTGCCGTGTTC-TGTTTCC-3′; PCR reaction conditions: 30 cycles of 94 °C (15 s), 55 °C (30 s) and 72 °C (40 s)]. Mice ($n$ = 17–18/genotype), 6–8 months of age, weighing 34.26 g ± 0.84 on average, were group-housed (3–5/cage) in Macrolon shoebox cages, with free access to food and water, in a humidity- and temperature (22 °C)-controlled vivarium on a 12-h light–dark cycle (lights off, 9:00 am). Mice were allowed to habituate to the testing environment for 1 h prior to all tests. Experiments were performed during the first half of the dark cycle. Procedures adhered to the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and were approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute. A single cohort of animals was used, per the following test sequence: elevated plus-maze – light–dark transfer –forced swim test – motor activity. Tests were spaced by at least 2 weeks, and the order of testing was chosen such that tests involving lower stress levels (elevated plus-maze and light–dark transfer) preceded those involving higher stress levels (forced swim). Non-computerized tests were videotaped and later scored by a single rater naïve to genotype. Slight differences in sample sizes across tests reflect procedural errors, including video recording failures or animals not completing testing due for example to falling off the apparatus, frequencies of which did not differ per genotype.

The elevated plus-maze test was performed as previously described [22,27]. The plus-maze consisted of two open and two closed arms (each 30 cm × 5 cm, 30 cm above the ground), extending horizontally at right angles from a central square (5 cm × 5 cm). The closed arms were enclosed by clear Plexiglas walls (30 cm high), whereas the open arms only had a 0.5 cm clear Plexiglas lip around their edges. Lighting on the open arms was ∼2 lx. Mice were placed in the central area facing an open arm and allowed to explore for 5 min. Open and closed arm entries (all four paws in the arm)

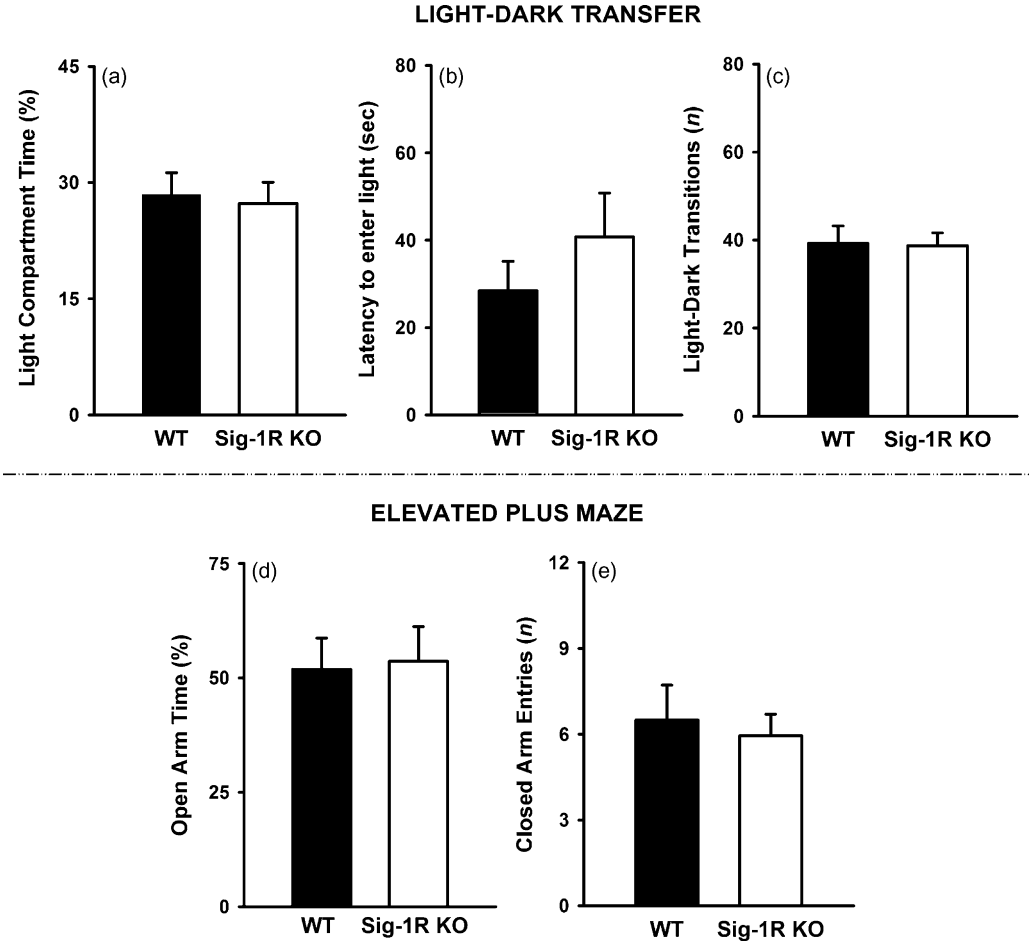


**Fig. 1.** Sig-1R KO mice do not differ from WT mice in the light–dark transfer or elevated plus-maze tests of anxiety-like behavior. *Light–dark transfer:* (a) Sig-1R KO mice ($n$ = 18) did not differ from their WT littermates controls ($n$ = 18) in the % of time spent in the light side of the light–dark box. (b) Upon initial placement in the dark side of the light–dark box, latency to first entry into the light side did not differ between Sig-1R KO and WT mice. (c) Sig-1R KO mice made the same number of transitions between sides of the light–dark box as did WT mice. *Elevated plus-maze*: (d) Sig-1R KO mice ($n$ = 17) did not differ from their WT littermates controls ($n$ = 18) in the % of time spent in the open arms of the maze, a measure of anxiety-like behavior. (e) Sig-1R KO and WT mice made the same number of entries into the closed arms of the maze, a measure of general motor activity. Data represent mean + SEM.

and time spent in the open arms, closed arms, and center square were scored. The % open arm time, an inverse measure of anxiety-like behavior, was calculated as [time in open arms/(total time in arms) × 100] [48].

The light–dark transfer test was performed as described previously [3,4,9] with minor modifications. The test apparatus was a Plexiglas rectangular box divided into two unequal compartments by a black Plexiglas partition with a small hole at the base (7.5 cm × 7.5 cm). The smaller compartment (14.5 cm × 27 cm × 26.5 cm) was dark (~0 lx), and the larger compartment (28.5 cm × 27 cm × 26.5 cm) was brightly illuminated (900 lx) with a 75 W light source located above it. To assess initial emergence behavior, mice were placed in the center of the dark compartment facing away from the partition to initiate the test session. The latency to enter the light compartment, the number of transitions between light and dark compartments and the % of time spent in the light compartment during each 10-min test session were scored.

Forced swim testing was adapted from the behavioral despair test described by Porsolt [39,40], using a larger diameter cylinder to increase sensitivity, as described previously [8,45]. Under light and within the first half of the dark cycle, mice were individually placed in two clear polypropylene cylinders (38 cm tall, 27 cm diameter; Cambro, Huntington Beach, CA) that were separated from one another by an opaque screen and which contained 23–25 °C water 30 cm deep to prevent the mouse's tail from touching the cylinder bottom [12,13]. The water was changed between subjects. A subject's behavior was scored for the last 4 min of the 6-min test session [39,40] via a previously validated time-sampling method in which the presence of immobility, swimming, or climbing was rated at 5-s intervals [12].

The motor activity apparatus consisted of 16 wire-mesh cages with disposable cardboard floors (20 cm × 25 cm × 36 cm), each equipped with two horizontal infrared photocell beams situated along the long axis of the cage, 2 cm above the floor and 16 cm from one another. Mice were individually placed into the unfamiliar apparatus during the first half of the dark cycle, and photocell interruptions were recorded automatically by a computer throughout the 10-min testing period with white noise (70 dB) present.

In the forced swim and motor behavior tests, genotype comparisons involved a two-way mixed design analysis of variance (ANOVA) on incremental data; genotype was a between-subjects factor and time a within-subjects factor. Differences between the two genotypes at each time point were analyzed using Student's unpaired *t*-test. Genotype differences in the light–dark transfer and elevated plus-maze tests were analyzed using Student's unpaired *t*-test.

In the light–dark transfer test of anxiety-like behavior, no significant genotype effects were found in the % of time spent in the light compartment of the apparatus [$t(1,34) = 0.28$; n.s.] (Fig. 1a), in the latency to first enter into the light compartment [$t(1,34) = 1.02$; n.s.] (Fig. 1b), or in the total number of transitions between compartments [$t(1,34) = 0.10$; n.s.] (Fig. 1c). Similarly, in the elevated plus-maze test, no significant genotype effects were found in the % of time spent on the open arms [$t(1,33) = 0.17$; n.s.] (Fig. 1d), a measure of anxiety-like behavior, or in the number of entries into the closed arms [$t(1,33) = 0.38$; n.s.] (Fig. 1e), a measure of non-specific motor activity.

In the forced swim test, Sig-1R KO mice showed significantly greater immobility [$F(1,32) = 4.39$; $p < 0.05$] (Fig. 2a) and less swimming than WT mice [$F(1,32) = 6.62$; $p < 0.05$] (Fig. 2b), a depressive-like phenotype. Pairwise comparisons showed that the two genotypes differed significantly during minutes 5 and 6 of the test session for both measures, leading to different cumulative scores. Sig-1R KO and WT showed similar levels of climbing [$F(1,32) = 0.01$; n.s.] (Fig. 2c).

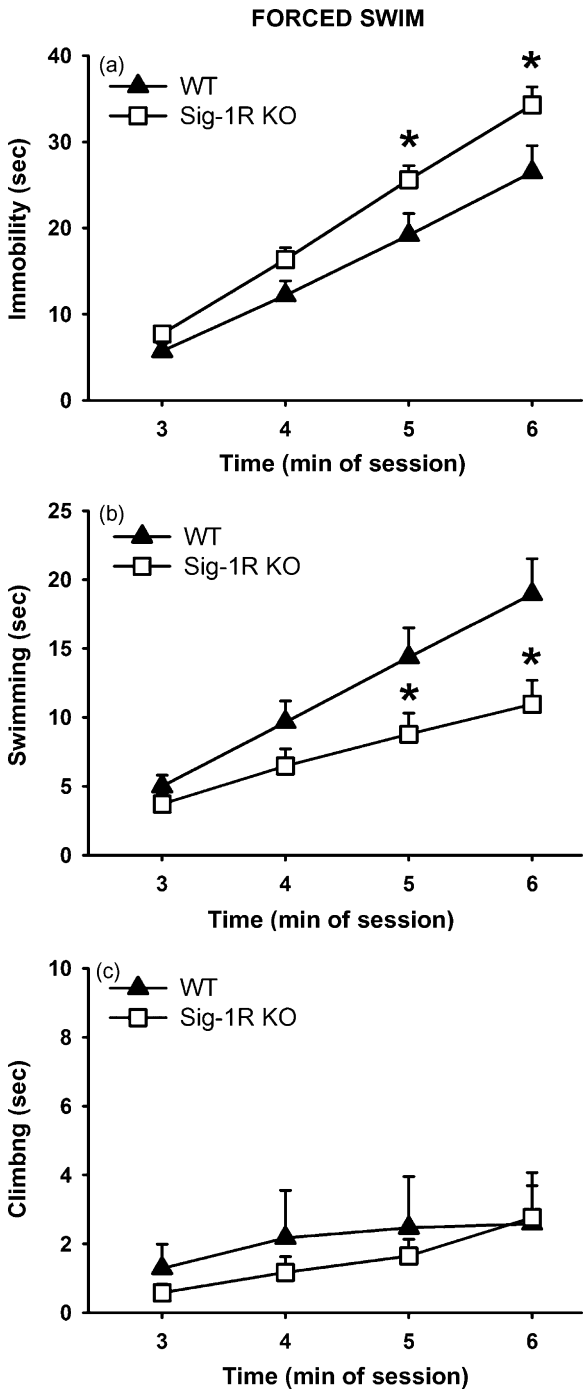


**Fig. 2.** Sig-1R KO mice exhibit increased depressive-like behavior in the forced swim test. (a) Sig-1R KO mice ($n = 17$) showed more immobility behavior than WT mice. (b) Sig-1R KO mice exhibited less swimming behavior than WT mice. (c) Sig-1R KO mice did not differ in climbing behavior from WT mice. Note *y*-axis scale differences. Data represent mean + SEM. *$p < 0.05$ (unpaired *t*-test).

The motor activity of the two genotypes in an unfamiliar environment did not differ across the 10-min observation period [$F(1,34) = 0.24$; n.s.], as shown in Fig. 3. The duration of the observation period was chosen to match the duration of the longest behavioral test (light–dark transfer) and to encompass the time frame of forced swim testing (minutes 3–6).

The present results show that mice that lack Sig-1R due to retroviral disruption of the Oprs1 gene show a depressive-like, but not anxiogenic-like, phenotype. Sig-1R KO mice exhibited a 30–35% increase in forced swim immobility time compared to WT mice,

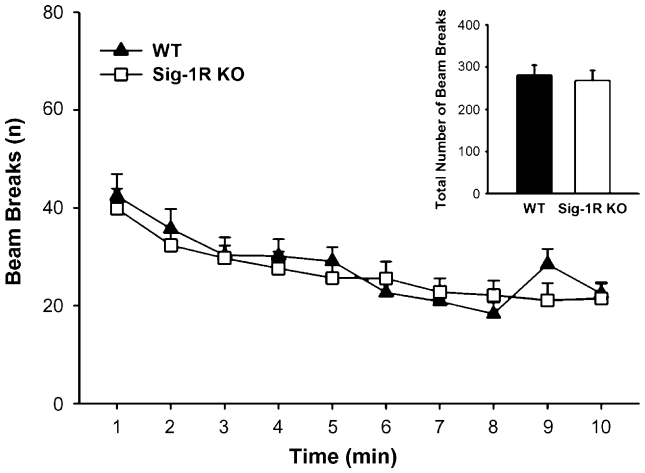


**Fig. 3.** Sig-1R KO mice do not differ from WT mice in motor activity in an unfamiliar environment. Sig-1R KO mice ($n = 18$) did not differ from their WT littermate controls ($n = 17$) in the number of beam breaks across the testing period. The inset shows the cumulative number of beam breaks in the whole 10 min. Data represent mean + SEM.

in the context of normal levels of climbing and normal levels of general motor activity in two other novel environments, the motor activity and elevated plus-maze tests. The depressive-like phenotype of Sig-1R KO mice is reciprocally consistent with the replicated finding that numerous Sig-1R agonists, including (+)-pentazocine, DTG, SA-4503, igmesine, and novel compounds of the UMB series, as well as neurosteroids such as dehydroepiandrosterone sulfate and pregnenolone, reduce immobility time in the forced swim and tail suspension tests in a Sig-1R antagonist reversible manner [1,15,16,29,41,46,47,49]. In addition, for several clinically used antidepressants, binding with the Sig-1R is important for their antidepressant-like activity in animal models [14,16,49].

The mechanism by which Sig-1Rs may modulate antidepressant-like behavior is not yet clear, but the present and previous results raise the hypothesis that modulation of serotonergic transmission may be involved. Sig-1R KO mice showed selective reductions in swimming, and not climbing, behavior in the forced swim test. Accordingly, Detke and co-workers [10,12] previously showed in the rat forced swim test that selective serotonin reuptake inhibitors and serotonin 1A receptor agonists selectively increase swimming, but not climbing, behavior, whereas tricyclic antidepressants and selective norepinephrine reuptake inhibitors preferentially increase climbing, but not swimming, behavior. The generalizability of this neuropharmacological specificity to the mouse forced swim test remains uncertain. However, also supporting the hypothesis that the increased depressive-like behavior observed in Sig-1R KO mice may relate to deficits in serotonergic neuronal activity, electrophysiological studies showed that SigR agonists, such as (+)-pentazocine and DTG, increase the firing of serotonergic neurons in the dorsal raphe nucleus, leading to an enhancement of serotonergic neurotransmission [5]. Follow-up molecular studies of serotonergic function and of the responsivity of Sig-1R KO mice to antidepressant-like activity of selective serotonin vs. noradrenergic reuptake inhibitors can help evaluate this hypothesis further.

Another interpretation is that the depressive-like behavior of Sig-1R KO mice might result from a dysregulated endoplasmic reticulum (ER) stress response. Growing evidence indicates that cellular stress signaling and ER stress specifically are involved not only in the pathophysiology of neurodegenerative diseases but also in that of mood disorders (for a review see [51]). Furthermore, mood-stabilizing drugs, such as valproate and lithium, have been demonstrated to increase the expression of ER chaperones, which have neuroprotective properties and are induced in conditions of ER stress [25,21]. Because Sig-1Rs are putative ligand-operated receptor chaperones that counteract ER stress (e.g., in response to calcium signaling), Sig-1Rs have been proposed to be cytoprotective [19]. The depressive-like behavior in Sig-1R KO mice might arise from the inability of these mice to respond efficiently to ER stress that can occur during signal transduction, leading to impaired neuronal function.

In summary, the present results with Sig-1R KO mutants implicate a role for Sig-1Rs in depressive-like behavior, findings which further validate Sig-1R agonists as potential therapeutics for depressive disorders.

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## References

[1] Akunne HC, Zoski KT, Whetzel SZ, Cordon JJ, Brandon RM, Roman F, et al. Neuropharmacological profile of a selective sigma ligand, igmesine: a potential antidepressant. Neuropharmacology 2001;41:138–49.
[2] Alonso G, Phan V, Guillemain I, Saunier M, Legrand A, Anoal M, et al. Immunocytochemical localization of the sigma(1) receptor in the adult rat central nervous system. Neuroscience 2000;97:155–70.
[3] Anseloni VZ, Motta V, Lima G, Brandao ML. Behavioral and pharmacological validation of the elevated plus maze constructed with transparent walls. Braz J Med Biol Res 1995;28:597–601.
[4] Bailey KR, Pavlova MN, Rohde AD, Hohmann JG, Crawley JN. Galanin receptor subtype 2 (GalR2) null mutant mice display an anxiogenic-like phenotype specific to the elevated plus-maze. Pharmacol Biochem Behav 2007;86:8–20.
[5] Bermack JE, Debonnel G. Modulation of serotonergic neurotransmission by short- and long-term treatments with sigma ligands. Br J Pharmacol 2001;134:691–9.
[6] Bouchard P, Quirion R. [3H]1, 3-di(2-tolyl)guanidine and [3H](+)pentazocine binding sites in the rat brain: autoradiographic visualization of the putative sigma1 and sigma2 receptor subtypes. Neuroscience 1997;76:467–77.
[7] Cendan CM, Pujalte JM, Portillo-Salido E, Montoliu L, Baeyens JM. Formalin-induced pain is reduced in sigma(1) receptor knockout mice. Eur J Pharmacol 2005;511:73–4.
[8] Chen A, Zorrilla E, Smith S, Rousso D, Levy C, Vaughan J, et al. Urocortin 2-deficient mice exhibit gender-specific alterations in circadian hypothalamus-pituitary-adrenal axis and depressive-like behavior. J Neurosci 2006;26:5500–10.
[9] Crawley J, Goodwin FK. Preliminary report of a simple animal behavior model for the anxiolytic effects of benzodiazepines. Pharmacol Biochem Behav 1980;13:167–70.
[10] Cryan JF, Valentino RJ, Lucki I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. Neurosci Biobehav Rev 2005;29:547–69.
[11] DeCoster MA, Klette KL, Knight ES, Tortella FC. Sigma receptor-mediated neuroprotection against glutamate toxicity in primary rat neuronal cultures. Brain Res 1995;671:45–53.
[12] Detke MJ, Rickels M, Lucki I. Active behaviors in the rat forced swimming test differentially produced by serotonergic and noradrenergic antidepressants. Psychopharmacology (Berl) 1995;121:66–72.
[13] Detke MJ, Lucki I. Detection of serotonergic and noradrenergic antidepressants in the rat forced swimming test: the effects of water depth. Behav. Brain Res 1996;73:43–6.
[14] Dhir A, Kulkarni SK. Involvement of sigma-1 receptor modulation in the antidepressant action of venlafaxine. Neurosci Lett 2007;420:204–8.
[15] Dhir A, Kulkarni S. Involvement of sigma (sigma1) receptors in modulating the anti-depressant effect of neurosteroids (dehydroepiandrosterone or pregnenolone) in mouse tail-suspension test. J Psychopharmacol 2008;22:691–6.
[16] Dhir A, Kulkarni SK. Possible involvement of sigma-1 receptors in the anti-immobility action of bupropion, a dopamine reuptake inhibitor. Fundam Clin Pharmacol 2008;22:387–94.
[17] Hanner M, Moebius FF, Flandorfer A, Knaus HG, Striessnig J, Kempner E, et al. Purification, molecular cloning, and expression of the mammalian sigma1-binding site. Proc Natl Acad Sci USA 1996;93:8072–7.

[18] Hayashi T, Su TP. The potential role of sigma-1 receptors in lipid transport and lipid raft reconstitution in the brain: implication for drug abuse. Life Sci 2005;77:1612–24.
[19] Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival. Cell 2007;131:596–610.
[20] Hellewell SB, Bowen WD. A sigma-like binding site in rat pheochromocytoma (PC12) cells: decreased affinity for (+)-benzomorphans and lower molecular weight suggest a different sigma receptor form from that of guinea pig brain. Brain Res 1990;527:244–53.
[21] Hiroi T, Wei H, Hough C, Leeds P, Chuang DM. Protracted lithium treatment protects against the ER stress elicited by thapsigargin in rat PC12 cells: roles of intracellular calcium, GRP78 and Bcl-2. Pharmacogenomics J 2005;5:102–11.
[22] Holmes A, Yang RJ, Crawley JN. Evaluation of an anxiety-related phenotype in galanin overexpressing transgenic mice. J Mol Neurosci 2002;18:151–65.
[23] Itzhak Y, Kassim CO. Clorgyline displays high affinity for sigma binding sites in C57BL/6 mouse brain. Eur J Pharmacol 1990;176:107–8.
[24] Kamei H, Kameyama T, Nabeshima T. (+)-SKF-10,047 and dextromethorphan ameliorate conditioned fear stress through the activation of phenytoin-regulated sigma 1 sites. Eur J Pharmacol 1996;299:21–8.
[25] Kim AJ, Shi Y, Austin RC, Werstuck GH. Valproate protects cells from ER stress-induced lipid accumulation and apoptosis by inhibiting glycogen synthase kinase-3. J Cell Sci 2005;118:89–99.
[26] Langa F, Codony X, Tovar V, Lavado A, Gimenez E, Cozar P, et al. Generation and phenotypic analysis of sigma receptor type I (sigma 1) knockout mice. Eur J Neurosci 2003;18:2188–96.
[27] Lu X, Ross B, Sanchez-Alavez M, Zorrilla EP, Bartfai T. Phenotypic analysis of GalR2 knockout mice in anxiety- and depression-related behavioral tests. Neuropeptides 2008;42:387–97.
[28] Matsumoto RR, Liu Y, Lerner M, Howard EW, Brackett DJ. Sigma receptors: potential medications development target for anti-cocaine agents. Eur J Pharmacol 2003;469:1–12.
[29] Matsuno K, Kobayashi T, Tanaka MK, Mita S. Sigma 1 receptor subtype is involved in the relief of behavioral despair in the mouse forced swimming test. Eur J Pharmacol 1996;312:267–71.
[30] Maurice T, Hiramatsu M, Itoh J, Kameyama T, Hasegawa T, Nabeshima T. Low dose of 1,3-di(2-tolyl)guanidine (DTG) attenuates MK-801-induced spatial working memory impairment in mice. Psychopharmacology (Berl) 1994;114:520–2.
[31] Maurice T, Lockhart BP. Neuroprotective and anti-amnesic potentials of sigma (sigma) receptor ligands. Prog Neuropsychopharmacol Biol Psychiatry 1997;21:69–102.
[32] Maurice T, Martin-Fardon R, Romieu P, Matsumoto RR. Sigma(1) (sigma(1)) receptor antagonists represent a new strategy against cocaine addiction and toxicity. Neurosci Biobehav Rev 2002;26:499–527.
[33] Mei J, Pasternak GW. Molecular cloning and pharmacological characterization of the rat sigma1 receptor. Biochem Pharmacol 2001;62:349–55.
[34] Moebius FF, Burrows GG, Hanner M, Schmid E, Striessnig J, Glossmann H. Identification of a 27-kDa high affinity phenylalkylamine-binding polypeptide as the sigma 1 binding site by photoaffinity labeling and ligand-directed antibodies. Mol Pharmacol 1993;44:966–71.
[35] Narita N, Hashimoto K, Tomitaka S, Minabe Y. Interactions of selective serotonin reuptake inhibitors with subtypes of sigma receptors in rat brain. Eur J Pharmacol 1996;307:117–9.
[36] Noda Y, Kamei H, Kamei Y, Nagai T, Nishida M, Nabeshima T. Neurosteroids ameliorate conditioned fear stress: an association with sigma receptors. Neuropsychopharmacology 2000;23:276–84.
[37] Pan YX, Mei J, Xu J, Wan BL, Zuckerman A, Pasternak GW. Cloning and characterization of a mouse sigma1 receptor. J Neurochem 1998;70:2279–85.
[38] Phan VL, Urani A, Sandillon F, Privat A, Maurice T. Preserved sigma1 (sigma1) receptor expression and behavioral efficacy in the aged C57BL/6 mouse. Neurobiol Aging 2003;24:865–81.
[39] Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. Nature 1977;266:730–2.
[40] Porsolt RD, Brossard G, Hautbois C, Roux S. Rodent models of depression: forced swimming and tail suspension behavioral despair tests in rats and mice. Curr Protoc Neurosci; 2001. p. 10A [Chapter 8, Unit 8].
[41] Reddy DS, Kaur G, Kulkarni SK. Sigma (sigma1) receptor mediated antidepressant-like effects of neurosteroids in the Porsolt forced swim test. Neuroreport 1998;9:3069–73.
[42] Sabino V, Cottone P, Zhao Y, Iyer MR, Steardo Lj, Steardo L, et al. The sigma receptor antagonist BD-1063 decreases ethanol intake and reinforcement in animal models of excessive drinking. Neuropsychopharmacology; in press, doi:10.1038/npp.2008.192.
[43] Schmidt A, Lebel L, Koe BK, Seeger T, Heym J. Sertraline potently displaces (+)-[3H]3-PPP binding to sigma sites in rat brain. Eur J Pharmacol 1989;165:335–6.
[44] Seth P, Fei YJ, Li HW, Huang W, Leibach FH, Ganapathy V. Cloning and functional characterization of a sigma receptor from rat brain. J Neurochem 1998;70:922–31.
[45] Sunal R, Gumusel B, Kayaalp SO. Effect of changes in swimming area on results of "behavioral despair test". Pharmacol Biochem Behav 1994;49:891–6.
[46] Ukai M, Maeda H, Nanya Y, Kameyama T, Matsuno K. Beneficial effects of acute and repeated administrations of sigma receptor agonists on behavioral despair in mice exposed to tail suspension. Pharmacol Biochem Behav 1998;61:247–52.
[47] Urani A, Roman FJ, Phan VL, Su TP, Maurice T. The antidepressant-like effect induced by sigma(1)-receptor agonists and neuroactive steroids in mice submitted to the forced swimming test. J Pharmacol Exp Ther 2001;298:1269–79.
[48] Wall PM, Messier C. Ethological confirmatory factor analysis of anxiety-like behaviour in the murine elevated plus-maze. Behav Brain Res 2000;114:199–212.
[49] Wang J, Mack AL, Coop A, Matsumoto RR. Novel sigma (sigma) receptor agonists produce antidepressant-like effects in mice. Eur Neuropsychopharmacol 2007;17:708–16.
[50] Weber E, Sonders M, Quarum M, McLean S, Pou S, Keana JF. 1,3-Di(2-[5-3H]tolyl)guanidine: a selective ligand that labels sigma-type receptors for psychotomimetic opiates and antipsychotic drugs. Proc Natl Acad Sci USA 1986;83:8784–8.
[51] Yoshida H. ER stress and diseases. FEBS J 2007;274:630–58.