Tramadol and another atypical opioid meperidine have exaggerated serotonin syndrome behavioural effects, but decreased analgesic effects, in genetically deficient serotonin transporter (SERT) mice

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Abstract
The serotonin syndrome is a potential side-effect of serotonin-enhancing drugs, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs). We recently reported a genetic mouse model for the serotonin syndrome, as serotonin transporter (SERT)-deficient mice have exaggerated serotonin syndrome behavioural responses to the MAOI tranylcypromine and the serotonin precursor 5-hydroxy-L-tryptophan (5-HTP). As numerous case reports implicate the atypical opioids tramadol and meperidine in the development of the human serotonin syndrome, we examined tramadol and meperidine as possible causative drugs in the rodent model of the serotonin syndrome in SERT wild-type (+/+), heterozygous (+/−) and knockout (−/−) mice. Comparisons were made with SERT mice treated with either vehicle or morphine, an opioid not implicated in the serotonin syndrome in humans. Here we show that tramadol and meperidine, but not morphine, induce serotonin syndrome-like behaviours in mice, and we show that this response is exaggerated in mice lacking one or two copies of SERT. The exaggerated response to tramadol in SERT−/− mice was blocked by pretreatment with the 5-HT1A antagonist WAY 100635. Further, we show that morphine-, meperidine- and tramadol-induced analgesia is markedly decreased in SERT−/− mice. These studies suggest that caution seems warranted in prescribing or not warning patients receiving SSRIs or MAOIs that dangerous side-effects may occur during concurrent use of tramadol and similar agents. These findings suggest that it is conceivable that there might be increased vulnerability in individuals with SERT polymorphisms that may reduce SERT by more than 50%, the level in SERT−/− mice.

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Key words: Hot-plate analgesia, meperidine, morphine, serotonin syndrome, serotonin transporter knockout mice, tramadol.

Introduction
The serotonin syndrome typically occurs following combinations of serotonin-enhancing drugs, including frequently prescribed antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs), taken even weeks apart (Gillman, 2006; Isbister & Buckley, 2005). Numerous case reports also implicate atypical opioids, including tramadol and meperidine (pethidine), as causative drugs in the serotonin syndrome (Altman & Manos, 2007; Choong & Ghiculescu, 2008; Das et al. 2008; Dougherty et al. 2002; Garrett, 2004; Gillman, 2005; Gnanadesigan et al. 2005; Houlihan, 2004; Kesavan & Sobala, 1999; Lantz et al. 1998; Mason & Blackburn, 1997; Mittino et al. 2004; Tissot, 2003; Vizcaychipi et al. 2007). In addition to their relatively weak actions on opioid receptors, tramadol, meperidine and other atypical opioids affect the reuptake and release of serotonin and norepinephrine (Dayer et al. 1994; Hennes et al. 1982; Raffa et al. 1992). (+)-Tramadol is a racemic mixture of (+)-tramadol, which has weak effects at μ-opioid receptors (K<sub>i</sub>=2.1 μM)
and reduces serotonin reuptake \((K_i=0.99 \mu M)\), and \((-\)-)tramadol, which reduces norepinephrine uptake \((K_i=0.79 \mu M)\) (Bamigbade et al. 1997; Driessen & Reimann, 1992; Hennies et al. 1982; Raffa et al. 1992).

In the rodent model of the serotonin syndrome, serotonin-enhancing drugs induce behaviours including head weaving, forepaw treading, backward movement, low body posture, hind-limb abduction and tremor (Izumi et al. 2006; Kennett et al. 1985; Sternbach, 1991). We recently reported a genetic mouse model for the serotonin syndrome, as constitutive serotonin transporter (SERT)-deficient mice produced by homologous recombination in embryonic stem (ES) cells have exaggerated serotonin syndrome behavioural responses to serotonin-enhancing drugs including the MAOI tranylcypromine and the serotonin precursor 5-hydroxy-L-tryptophan (5-HTP) (Fox et al. 2007, 2008). To our knowledge, the ability of tramadol and related agents to induce serotonin syndrome behaviours in rodents has not been experimentally evaluated.

In the present study, we examined tramadol and meperidine as possible causative drugs in the rodent model of the serotonin syndrome in SERT wild-type \((+/+)\), heterozygous \((+/-)\) and knockout \((-/-)\) mice, and comparisons were made with SERT mice treated with either vehicle or morphine, an opioid not implicated in the serotonin syndrome in humans (Gillman, 2005).

Serotonin syndrome behaviours in mice, including the exaggerated 5-HTP-induced serotonin syndrome behavioural responses in SERT-deficient mice (Fox et al. 2007), are mediated by postsynaptic 5-HT1A receptors (Lucki et al. 1984; Smith & Peroutka, 1986; Yamada et al. 1988). As tramadol is known to have some effects at 5-HT1A receptors (Berrocoso et al. 2006; Rojas-Corrales et al. 2000, 2005), we also determined the possible contribution of 5-HT1A receptors in tramadol-induced serotonin syndrome behaviours in SERT-deficient mice. Finally, as tramadol is a frequently prescribed and effective analgesic medication, we also determined the analgesic effects of tramadol, in addition to meperidine and morphine, in SERT-deficient mice.

Materials and methods

Animals

Subjects were female SERT mice \((+/+, +/-\) and \(-/-\)\) produced by homologous recombination in ES cells as previously described (Bengel et al. 1998), and currently the product of \(\sim 20–24\) heterozygous backcrosses with wild-type mice on a C57BL/6J genetic background. Female C57BL/6J mice were purchased from the Jackson Laboratory (USA). The animals weighed \(\sim 20–35\) g at the beginning of the experiments, and were housed in groups of \(3–5\) per cage with food and water available \(ad\) \(libitum\). The animals were maintained on a 12-h light/dark cycle (lights on 06:00 hours) in a facility approved by the American Association for Accreditation of Laboratory Animal Care. All experiments adhered to the guidelines of the National Institutes of Health, and were approved by the National Institute of Mental Health Animal Care and Use Committee.

Drugs

\((\pm)\)-Tramadol, meperidine, morphine and the selective 5-HT1A receptor antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclohexanecarboxamide maleate salt (WAY 100635) were purchased from Sigma Chemical Company (St Louis, USA). All drugs were prepared in saline and were administered by intraperitoneal (i.p.) injection.

Procedure

On test days, animals were moved to the testing room in their home cage 1 h prior to testing to allow for habituation to the environment. All experiments were carried out between 10:00 and 13:00 hours.

Serotonin syndrome behaviours

Animals were placed in a large Plexiglas cylinder, and after 15 min of habituation were administered vehicle, tramadol, meperidine or morphine (60 mg/kg for each of these drugs). When 5-HT1A mediation of tramadol-induced behavioural changes was examined, mice were pretreated with either vehicle or the selective 5-HT1A antagonist WAY 100635 (1 mg/kg) 30 min prior to tramadol (60 mg/kg). This dose of WAY 100635 was selected based on previous studies (Fox et al. 2007, 2008). Behavioural assessments were made based on previous methods (Fox et al. 2007, 2008; Izumi et al. 2006; Kennett et al. 1985). Specifically, behaviours associated with the rodent serotonin syndrome were recorded for five 1-min periods at 5-min intervals starting 5 min after drug administration for 30 min. In each assessment period, the following behaviours were recorded: (a) intermittent behaviours included head weaving, forepaw treading and backward movement (scored on a 5-point scale; 0 = absent, 1 = present once, 2 = present several times, 3 = present frequently, 4 = present continuously); (b) continuous behaviours included hind-limb abduction, tremor and low body posture (scored on a 5-point scale; 0 = absent,
scores for Straub tail are presented separately. Straub tail was assessed in the same manner as other continuous behaviours described above. Behavioural assessments were performed by observers blind to both the genotype and the drug condition.

**Hot-plate analgesia**

Analgesia was assessed using the hot-plate test. The hot-plate apparatus (Columbus Instruments, USA) was maintained at 55.0 ± 0.1 °C, and was surrounded by a Plexiglas enclosure. Mice were placed individually on the hot plate, and the latency to lick their hind paw or jump was measured. Mice were removed immediately after a response was made, with a 30 s cut-off if no response occurred. Data are presented as the percent of the maximum possible effect (MPE):

$$\% \text{MPE} = \left( \frac{\text{test latency} - \text{average baseline latency}}{30 \text{s cut-off} - \text{average baseline latency}} \right) \times 100,$$

where the average baseline latency is the average of three baseline assessments taken prior to drug administration. Following the baseline assessments, mice were administered vehicle or morphine (30 mg/kg), tramadol (60 mg/kg) or meperidine (30 mg/kg) and analgesia was assessed every 15 min over a 45-min period. These doses were selected based on dose–response pilot studies performed in our laboratory (data not shown). The data presented are for the time-point where analgesia was greatest in SERT+/+ mice (morphine, 45 min; meperidine, 15 min; tramadol, 15 min).

**Statistical analyses**

For each experiment, data were analysed using one-way or two-way (genotype x drug condition) analyses of variance (ANOVAs). Significant main effects (one-way ANOVAs) or significant interactions (two-way ANOVAs) were followed by post-hoc comparisons between genotypes or between drug conditions using Tukey’s HSD pairwise comparisons. Significance was based on $p < 0.05$.

**Results**

**Serotonin syndrome behaviours**

For serotonin syndrome behaviours overall, there was a significant genotype x drug interaction [$F(6, 105) = 2.98$, $p = 0.01$] and significant main effects for genotype [$F(2, 105) = 21.56$, $p < 0.0001$] and for drug [$F(3, 105) = 45.31$, $p < 0.0001$]. Compared to their respective counterparts administered vehicle or morphine, SERT mice (+/+, +/− and −/−) administered either tramadol or meperidine displayed increased levels of serotonin syndrome behaviour overall (Fig. 1). This response was exaggerated in SERT+/− ($p = 0.023$) and SERT−/− mice ($p = 0.008$) administered tramadol, and in SERT−/− mice administered meperidine ($p = 0.001$),
Table 1. Individual serotonin syndrome behaviours (sum of scores) in SERT mice (+/+, +/− and −/−) administered tramadol or meperidine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Behaviour (sum of scores)</th>
<th>SERT+/+</th>
<th>SERT+/-</th>
<th>SERT−/-</th>
<th>One-way ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>d.f.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Head weaving</td>
<td>8.58±2.88</td>
<td>10.23±3.46</td>
<td>12.15±3.51*</td>
<td>2, 36</td>
</tr>
<tr>
<td></td>
<td>Forepaw treading</td>
<td>2.00±2.20</td>
<td>1.39±1.66</td>
<td>3.31±3.92</td>
<td>2, 36</td>
</tr>
<tr>
<td></td>
<td>Backward movement</td>
<td>0.08±0.28</td>
<td>0.69±1.38</td>
<td>1.35±1.28*</td>
<td>2, 36</td>
</tr>
<tr>
<td></td>
<td>Hind-limb abduction</td>
<td>3.85±1.83</td>
<td>8.69±4.97*</td>
<td>9.92±5.83**</td>
<td>2, 36</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>2.85±3.06</td>
<td>4.04±2.85</td>
<td>2.54±1.93</td>
<td>2, 36</td>
</tr>
<tr>
<td></td>
<td>Low posture</td>
<td>4.65±3.92</td>
<td>10.46±5.80</td>
<td>8.39±6.09*</td>
<td>2, 36</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Head weaving</td>
<td>8.13±4.20</td>
<td>7.75±3.81</td>
<td>10.63±5.37</td>
<td>2, 21</td>
</tr>
<tr>
<td></td>
<td>Forepaw treading</td>
<td>3.75±3.81</td>
<td>1.75±1.75</td>
<td>5.00±4.11</td>
<td>2, 21</td>
</tr>
<tr>
<td></td>
<td>Backward movement</td>
<td>0.63±0.74</td>
<td>0.63±1.19</td>
<td>1.38±1.60</td>
<td>2, 21</td>
</tr>
<tr>
<td></td>
<td>Hind-limb abduction</td>
<td>7.50±1.91</td>
<td>8.88±2.17</td>
<td>10.94±3.30*</td>
<td>2, 21</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>2.81±2.78</td>
<td>5.50±5.78</td>
<td>10.88±3.91**</td>
<td>2, 21</td>
</tr>
<tr>
<td></td>
<td>Low posture</td>
<td>3.38±2.31</td>
<td>5.94±4.26</td>
<td>10.79±4.23**</td>
<td>2, 21</td>
</tr>
</tbody>
</table>

Data represent the mean ± S.E.M., n = 8–13 per group.

* p < 0.05, ** p < 0.01 compared to SERT+/+ mice (Tukey post-hoc tests).

Effects of the selective 5-HT1A antagonist WAY 100635 on tramadol-induced serotonin syndrome behaviours

For the overall serotonin syndrome behavioural scores in a first study in purchased wild-type C57BL/6J mice, there was a significant main effect for drug [F(8, 18) = 17.96, p < 0.0001]. Tramadol again increased serotonin syndrome behaviours compared to vehicle-treated mice (p < 0.0001). Pretreatment with WAY 100635 had no effect on tramadol-induced behaviours in purchased wild-type mice (drug, mean ± S.D.) (vehicle: 6.1 ± 1.56; WAY 100635: 4.92 ± 2.99; vehicle + tramadol: 27.80 ± 9.50; WAY 100635 + tramadol: 25.33 ± 8.96).

In a separate study in SERT+/− and SERT−/− mice, there was a significant genotype × drug interaction for the overall serotonin syndrome behaviour scores [F(3, 54) = 5.85, p = 0.002], with a significant main effect for drug [F(3, 54) = 19.52, p < 0.0001] but not for genotype [F(1, 54) = 0.37, n.s.]. Again, tramadol induced serotonin syndrome behaviours in SERT+/− and SERT−/− mice compared to their vehicle-treated counterparts (Fig. 2). In SERT−/− mice, pretreatment with WAY 100635 decreased tramadol-induced behaviours to levels closely approximating those observed in vehicle-treated SERT−/− mice, suggesting that 5-HT1A receptors mediate tramadol-induced serotonin
Table 2. Straub tail (sum of scores) in SERT +/+ , +/− and −/− mice administered vehicle, morphine, tramadol or meperidine.

<table>
<thead>
<tr>
<th>Drug</th>
<th>SERT +/+</th>
<th>SERT +/−</th>
<th>SERT −/−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>0.22 ± 0.26</td>
<td>0.00 ± 0.00</td>
<td>0.94 ± 1.49</td>
</tr>
<tr>
<td>Morphine</td>
<td>14.44 ± 4.71</td>
<td>17.33 ± 2.54</td>
<td>12.67 ± 3.82</td>
</tr>
<tr>
<td>Tramadol</td>
<td>8.88 ± 4.87</td>
<td>6.35 ± 4.25</td>
<td>10.19 ± 3.47</td>
</tr>
<tr>
<td>Meperidine</td>
<td>11.38 ± 2.85</td>
<td>10.75 ± 4.09</td>
<td>13.06 ± 4.24</td>
</tr>
</tbody>
</table>

Data represent the mean ± S.E.M.; n = 8–13 per group.
**p < 0.01, +++ p < 0.0001 compared to vehicle-treated mice of the same genotype; *p < 0.05, ** p < 0.001 compared to tramadol-treated mice of the same genotype; ***p < 0.01 compared to meperidine-treated mice of the same genotype (Tukey post-hoc tests).

Fig. 2. Overall serotonin syndrome behaviours (sum of scores) in SERT +/+ (■) and SERT −/− (□) mice administered vehicle, WAY 100635, vehicle + tramadol, or WAY 100635 + tramadol. Data represent the mean ± S.E.M., n = 5–8 per group.
* p < 0.05, ** p < 0.01 compared to SERT +/− mice in the same drug condition; † p < 0.05, ††† p < 0.001 compared to mice of the same genotype administered vehicle; ††† p < 0.01, †††† p < 0.001 compared to mice of the same genotype administered WAY 100635; † p < 0.05 compared to mice treated with vehicle + tramadol.

syndrome behaviours in SERT −/− mice. However, pretreatment with WAY 100635 did not alter tramadol-induced serotonin syndrome behaviours in SERT +/− mice, suggesting that a different mechanism underlies this exaggerated response in SERT +/− mice.

Hot-plate analgesia

Consistent with previous findings in SERT-deficient mice (Kayser et al. 2007; Palm et al. 2008), the average baseline latency to respond was similar between the three genotypes [data combined from all analgesia studies; F(2,275) = 1.70, n.s.] (Fig. 3). There were significant main effects of genotype for the latency to respond ( % MPE) in mice administered morphine

![Graph showing latency (percent of the maximum possible effect, % MPE) for different drugs and genotypes](image)

Fig. 3. Baseline hot-plate responses in SERT +/+ (■), SERT +/− (□) and SERT −/− (□) mice. Data represent the mean latency (percent of the maximum possible effect, % MPE) ± S.E.M., data combined from all analgesia studies.

[F(2,27) = 5.08, p = 0.014], tramadol [F(2,31) = 3.68, p = 0.038] and meperidine [F(2,28) = 3.98, p = 0.031]. In SERT −/− mice, morphine- (p = 0.014) and tramadol- (p = 0.045) induced analgesia were decreased ~64% and ~58%, respectively, compared to SERT +/+ mice, and meperidine-induced analgesia was decreased ~65% compared to SERT +/− mice (p = 0.027) (Fig. 4).

There was also a strong trend towards decreased morphine-induced analgesia in SERT +/− mice compared to SERT +/+ mice (p = 0.065).

Discussion

In the present study, we provide the first experimental evidence that the atypical opioids tramadol and meperidine induce serotonin syndrome-like behaviours in mice, and show that this response is exaggerated in mice lacking one or two copies of SERT (Fig. 1). Functional polymorphisms in SERT in humans, such as the SERT-linked polymorphic region (5-HTTLPR) and single nucleotide polymorphisms (SNPs) within it, can reduce SERT expression and its
function by ~50% or more (Hu et al. 2006; Lesch et al. 1996; Praschak-Rieder et al. 2007), similar to levels in SERT+/− mice. As such, the current findings might suggest an increased vulnerability to development of the serotonin syndrome in individuals with lesser-expressing SERT polymorphisms when taking tramadol or similar agents.

The serotonin syndrome is a not infrequent and potentially lethal side-effect of serotonin-enhancing drugs (such as SSRIs and MAOIs), which is associated with neuromuscular hyperactivity (e.g. tremor, myoclonus), autonomic hyperactivity (e.g. fever) and altered mental status (Dunkley et al. 2003; Gillman, 2006; Sternbach, 1991). As described, numerous case reports also implicate atypical opioids, including tramadol and meperidine, in the development of the serotonin syndrome. Such cases include individuals taking tramadol or meperidine in combination with other serotonin-enhancing drugs, including SSRIs and MAOIs (see Introduction). Importantly, a recent study shows a significant incidence of co-prescription of tramadol with MAOIs, SSRIs and other serotonin-enhancing drugs (Ringland et al. 2008). In this retrospective assessment of medical claims over a 4-yr period, ~8% of this population (~20 658 individuals) evidenced at least one incident of potential concurrent use of serotonergic medication combinations. Among the most common were tramadol with a SSRI or moclobemide, a reversible inhibitor of monoamine oxidase-A (RIMA) (Ringland et al. 2008).

In the present study, pretreatment with WAY 100635 did not alter serotonin syndrome behaviours observed in wild-type mice. In SERT+/− mice, which displayed exaggerated serotonin syndrome behavioural responses to tramadol, WAY 100635 pretreatment was also without effect. However, the exaggerated tramadol-induced serotonin syndrome behavioural response in SERT−/− mice was significantly attenuated by pretreatment with WAY 100635, suggesting mediation at post-synaptic 5-HT1A receptors, known to regulate these behaviours in wild-type mice (Lucki et al. 1984; Smith & Peroutka, 1986; Yamada et al. 1988), and the exaggerated 5-HTP-induced serotonin syndrome behavioural responses previously reported in SERT−/− mice (Fox et al. 2007). Together, these findings suggest that another mechanism underlies this exaggerated response in SERT+/− mice, a mechanism which is of importance to explore, and will require further studies. One possibility is that tramadol might be inducing this exaggerated serotonin syndrome behavioural response in SERT+/− mice by blocking SERT, thus increasing extracellular levels of serotonin, rather than by directly activating post-synaptic 5-HT1A receptors, which appears to underlie this response in SERT−/− mice. However, the site of action of these elevated serotonin levels in SERT+/− mice remains to be elucidated.

Tramadol is an effective analgesic medication, with fewer side-effects and lower abuse potential than more traditional opioids such as morphine. In the first tests of opioid analgesia in genetically deficient SERT mice, we report that morphine-, meperidine- and tramadol-induced analgesia is markedly decreased in SERT−/− mice, with a strong trend towards a decrease in morphine-induced analgesia in SERT−/− mice (Fig. 4). The mechanisms underlying the decreased analgesic effects of these typical and atypical opioids in SERT-deficient mice remain to be elucidated, but would seem to be of high interest.

There appear to be several different mechanisms of action underlying the analgesic effects of tramadol, which probably interact, and which are probably species and paradigm specific. For example, although the non-selective opioid antagonist naltrexone decreases the analgesic effects of tramadol in humans (Desmeules et al. 1996) and in rodents (Berrocoso et al. 2007; Raffa et al. 1992), this effect is only partial in some assessments. Further, tramadol retains its analgesic effects in µ-opioid knockout mice, an effect decreased in a gene–dose dependent manner (Ide et al.
2006). These studies suggest that the analgesic effects of tramadol are not solely mediated by the opioid system. To our knowledge, the number, binding and function of opioid receptors have not been examined in SERT-deficient mice.

A role for the norepinephrine system has also been described, as the $\alpha_2$-adrenoceptor antagonist yohimbine blocks tramadol-induced analgesia (Raffa et al. 1992), including the residual response in $\mu$-opioid knockout mice (Ide et al. 2006) in some analgesia paradigms. Other studies show that tramadol analgesia is markedly enhanced in $\alpha_2A$-adrenoceptor knockout mice (blocked by naloxone), and that the $\alpha_2$-adrenoceptor antagonists yohimbine and atipamezole potentiated the analgesic effects of tramadol in wild-type mice (Ozdogan et al. 2006). The only investigations of the norepinephrine system in SERT-deficient mice show that the anti-immobility effects of the norepinephrine transporter (NET) blocker desipramine and the SERT/NET blocker imipramine in the tail suspension test were retained in SERT $^{+/+}$ and SERT $^{-/-}$ mice (Holmes et al. 2002), and that there are no differences in [H]$\text{H}$-isoxeotine binding to NET in the CA3 area of the hippocampus in mice of the three SERT genotypes (Montanez et al. 2003). Together, these studies suggest an intact norepinephrine system in SERT-deficient mice, although specific noradrenergic receptors, including $\alpha_2$-adrenoceptors, have not yet been examined in SERT-deficient mice. As yohimbine might also have effects at 5-HT$_{1D}$ receptors (Hoyer et al. 1990; Millan et al. 2000), it might also be of interest to investigate a possible role for 5-HT$_{1D}$ receptors in the decreased analgesic responses reported here in SERT-deficient mice.

Roles for the serotonin system have also been noted in tramadol’s actions. For example, the selective 5-HT$_{1A}$ antagonist WAY 100635 (Berrocoso et al. 2006, 2007; Rojas-Corrales et al. 2005) and the 5-HT$_{1A}$ antagonist/\-adrenoceptor antagonist pindolol (Rojas-Corrales et al. 2000) increase the analgesic effects of tramadol, whereas the 5-HT$_{1A}$ agonist 8-OH-DPAT decreases tramadol-induced analgesia (Berrocoso et al. 2007; Rojas-Corrales et al. 2000). Yet other studies suggest a role for 5-HT$_{2A}$ receptors in tramadol-induced analgesia (Oliva et al. 2002; Xie et al. 2008). Numerous studies show alterations in several of serotonin’s 14-plus receptor subtypes in SERT-deficient mice, including decreased number and function of presynaptic 5-HT$_{1A}$ receptors (Bouali et al. 2003; Fox et al. 2008; Holmes et al. 2003; Li et al. 1999, 2000) and brain-area-dependent changes in 5-HT$_{2A}$ binding and function (Basselin et al. 2009; Li et al. 2003; Qu et al. 2005; Rioux et al. 1999).

Further studies are required in order to determine the mechanism underlying the decreased analgesic responses to tramadol, meperidine and morphine in SERT-deficient mice. For example, it will be of importance to determine the effects of pretreatment with 5-HT$_{1A}$ antagonists such as WAY 100635 and $\alpha_2$-adrenoceptor antagonists such as yohimbine on opioid-induced analgesia in SERT mice (+/+, +/− and −/−).

Several studies report that in addition to its analgesic effects, tramadol has effects in animal models of several psychiatric disorders. Tramadol is effective in animal models predictive of antidepressant efficacy; e.g. tramadol decreases immobility in the forced swim test and reverses the physical and behavioural alterations induced by unpredictable chronic mild stress (Berrocoso et al. 2006; Rojas-Corrales et al. 1998, 2002, 2004; Yalcin et al. 2005, 2007, 2008). Additionally, tramadol blocks the head-twitch response in mice induced by the serotonin precursor 5-HTP and the 5-HT$_{2A/C}$ agonist (±)-2,5-dimethoxy-4-iodophenyl-2-aminopropane (DOI) (Rojas-Corrales et al. 2007; Sun et al. 2003), suggested as an animal model for tics and Tourette syndrome (Dursun & Handley, 1996; Gaynor & Handley, 2001; Hayslett & Tizabi, 2005).

Importantly, findings in humans also suggest that tramadol may be an effective treatment in several neuropsychiatric illnesses, in particular in some patients who are refractory to traditional treatments. Specifically, these studies suggest that tramadol might be effective in treating depression (Reeves & Cox, 2008; Shapira et al. 2001; Spencer, 2000), potentiating the antidepressant effects of other medications including SSRIs (Fanelli & Montgomery, 1998), decreasing suicidal ideation (Spencer, 2000) and in treating obsessive–compulsive disorder (OCD) and Tourette syndrome (Goldsmith et al. 1999; Shapira et al. 1997a, b, 2001).

The current findings are important, as they suggest caution when using tramadol in the treatment of, or to augment SSRIs or other antidepressants in the treatment of, pain, depression, OCD, Tourette syndrome and other psychiatric disorders where these pro-serotonergic agents might be employed (Fanelli & Montgomery, 1998; Goldsmith et al. 1999; Reeves & Cox, 2008; Shapira et al. 1997a, b, 2001; Spencer, 2000). Similarly, caution seems warranted in prescribing or not warning patients receiving SSRIs or MAOIs, that dangerous side-effects may occur during concurrent use of tramadol and similar agents for their analgesic actions (Ringland et al. 2008). The current findings also suggest caution when prescribing tramadol and other atypical opioid medications to individuals with the
S or SS 5-HTTLPR, SERT polymorphisms that may reduce SERT by more than 50% (Hu et al. 1996; Lesch et al. 1996; Prasad et al. 2005), as these individuals might be at higher risk for developing the serotonin syndrome. Further, within this genetic mouse model, it is of high importance to investigate the effects of other drugs implicated in human cases of the serotonin syndrome, such as the antibiotic linezolid (Das et al. 2008; Packer & Berman, 2007), triptans used in the treatment of migraine (Bonetto et al. 2007), as well as St John’s Wort and other over-the-counter herbal remedies (Bonetto et al. 2007; Dannawi, 2002; Parker et al. 2001).

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Statement of Interest

None.

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