Synergistic Interaction between the Two Mechanisms of Action of Tapentadol in Analgesia


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ABSTRACT

The novel centrally acting analgesic tapentadol [(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride] combines two mechanisms of action, \( \mu \)-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI), in a single molecule. Pharmacological antagonism studies have demonstrated that both mechanisms of action contribute to the analgesic effects of tapentadol. This study was designed to investigate the nature of the interaction of the two mechanisms. Dose-response curves were generated in rats for tapentadol alone or in combination with the opioid antagonist naloxone or the \( \alpha_2 \)-adrenoceptor antagonist yohimbine. Two different pain models were used: 1) low-intensity tail-flick and 2) spinal nerve ligation. In each model, we obtained dose-effect relations to reveal the effect of tapentadol based on MOR agonism, NRI, and unblocked tapentadol. Receptor fractional occupation was determined from tapentadol’s brain concentration and its dissociation constant for each binding site. Tapentadol produced dose-dependent analgesic effects in both pain models, and its dose-effect curves were shifted to the right by both antagonists, thereby providing data to distinguish between MOR agonism and NRI. Both isobolographic analysis of occupation-effect data and a theoretically equivalent methodology determining interactions from the effect scale demonstrated very pronounced synergistic interaction between the two mechanisms of action of tapentadol. This may explain why tapentadol is only 2- to 3-fold less potent than morphine across a variety of preclinical pain models despite its 50-fold lower affinity for the MOR. This is probably the first demonstration of a synergistic interaction between the occupied receptors for a single compound with two mechanisms of action.

Introduction

Monoamine reuptake inhibitors (tricyclics, nontricyclic serotonin-noradrenaline reuptake inhibitors) are among the first-line treatment options for chronic pain. These drugs are generally tolerated relatively well. However, analgesic efficacy of such drugs is often not satisfactory (Fishbain, 2000). Opioids also play an important role in the treatment of chronic pain and can produce potent analgesia (Kalso et al., 2004). However, opioids are often faced with tolerability problems. In particular, gastrointestinal side effects such as nausea, vomiting, and constipation can be troublesome with opioid treatment (Moore and McQuay, 2005).

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ABBREVIATIONS: tapentadol, [(-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride; CI, confidence interval; CL, confidence limit; MPE, maximal possible effect; MOR, \( \mu \)-opioid receptor; NAT, noradrenaline transporter; NRI, noradrenaline reuptake inhibition; SNL, spinal nerve ligation.
and 2) it does so in a supra-additive/synergistic manner. Consistent with the rationale above, tapentadol has demonstrated potent analgesia in acute and chronic pain along with a substantially improved gastrointestinal side-effect profile in clinical studies (Hale et al., 2009; Hartrick et al., 2009; Hartrick, 2009).

There is preclinical and clinical evidence that opioid analgesia can indeed be augmented by noradrenergic compounds. For example, MOR agonists and noradrenaline reuptake inhibitors or α2-adrenoceptor agonists additively or synergistically produced analgesia after systemic and intrathecal administration in models of acute and chronic pain. The noradrenaline reuptake inhibitor desipramine increased morphine analgesia after systemic and intrathecal administration (Ossipov et al., 1982; Reimann et al., 1999), and systemic as well as spinal combination of morphine with the α2-adrenoceptor agonist clonidine resulted in synergistic antinociception (Ossipov et al., 1990; Fairbanks and Wilcox, 1999). In clinical settings, morphine analgesia was potentiated by systemic tricyclic antidepressants (Levine et al., 1986; Ventafridda et al., 1990) and spinal/epidural clonidine (Motsch et al., 1990; Anzai and Nishikawa, 1995).

Isobolographic analysis is a method traditionally used to establish whether an interaction of two agonist drugs is subadditive, additive, or supra-additive/synergistic. In such applications the individual compounds are administered in graded doses by themselves and subsequently in dose combinations that are often fixed-ratio combinations of the two compounds (Tallarida, 2001, 2006, 2007; Tallarida et al., 2003; Tallarida and Raffa, 2010). In the present case, we were concerned with a single compound whose effect is mediated through two distinct mechanisms. The analysis used therefore consisted of a two-pronged approach: 1) a comparison of the observed and (calculated) additive effect magnitudes and 2) the use of isoboles based on the fractional occupancy of each binding site. Pharmacological antagonism studies have shown that both mechanisms of action of tapentadol (MOR, NRI) contribute to its analgesic effect (Tzschenkte et al., 2006, 2007; Schröder et al., 2010). Accordingly, receptor-specific antagonists were used to distinguish between the effects mediated by each component in relation to dose. Toward that end, dose-response curves were generated in the low-intensity tail-flick model of acute nociception and the spinal nerve ligation (SNL) model of chronic mononeuropathic pain in rats for tapentadol alone, tapentadol in combination with the MOR antagonist naloxone, and tapentadol in combination with the α2-adrenoceptor antagonist yohimbine. The data from these experiments have been published in part previously in a different form and context (Schröder et al., 2010). In additional experiments, for purposes of converting tapentadol doses to receptor occupation, brain concentrations of tapentadol associated with each intraperitoneal dose were determined in satellite groups of rats at the same time point as the analgesic effect was quantified in the low-intensity tail-flick test. This allowed a correlation of tapentadol brain concentrations with a given analgesic effect that was caused by both mechanisms, exclusively because of MOR agonism (under yohimbine antagonism) or exclusively because of NRI (under naloxone antagonism).

Materials and Methods

Behavioral Testing

Animals. Male Sprague-Dawley rats (Janvier, Le Genest St Isle, France) were housed under a 12:12-h light-dark cycle (lights on at 6:00 AM), room temperature 20 to 24°C, relative air humidity 35 to 70%, 15 air changes per hour, and air movement less than 0.2 m/s. The animals had free access to standard laboratory food and tap water. There were at least 5 days between the delivery of the animals and behavioral testing. Average weights were 160 to 240 g. All experiments were conducted according to the Declaration of Helsinki and the guidelines of the International Association for the Study of Pain (Zimmermann, 1983) and the German Animal Welfare Law.

Experimental Procedures

Animals were assigned randomly to treatment groups. Different doses and vehicle were tested in a randomized fashion. Although the operators performing the behavioral tests were not formally “blinded” with respect to the treatment, they were not aware of the study hypothesis or the nature of the differences between drugs.

Low-Intensity Tail-Flick Test. The tail-flick test was carried out in rats using a modification of the method described by D’Amour and Smith (1941). The tail-flick latency, defined by the time (in seconds) to withdraw the tail from a radiant heat source, was measured using a semiautomated device (Rhema Labotechnik, Hofheim, Germany). The rat was placed in a Plexiglas restrainer, and a low-intensity radiant heat beam was focused onto the dorsal surface of the tail root. The stimulus intensity was adjusted to result in a mean predrug control latency of 7 s, thus also allowing a supraspinal modulation of the spinally mediated acute nociceptive reflex. A cutoff time of 30 s was applied to avoid tissue damage. The increase in tail-flick latency was defined as antinociception and calculated as the percentage of maximal possible effect (MPE) according to the following formula: $\text{MPE} \% = \left( \frac{t_c - t_i}{t_{\text{cutoff}} - t_i} \right) \times 100\%$, where $t_c$ is withdrawal latency, $t_i$ is control latency, and $t_{\text{cutoff}}$ is cutoff time.

Animals were tested before and 30 min after intravenous administration of tapentadol or vehicle. Naloxone (1 mg/kg) and yohimbine (2.15 mg/kg) or the respective vehicle was given intraperitoneally 10 min before tapentadol.

In additional experiments focusing to correlate receptor occupancy with analgesic effects, animals were tested before and 10, 20, and 30 min after intraperitoneal administration of tapentadol or vehicle. The antagonist naloxone (1 mg/kg), yohimbine (4.64 mg/kg), or the respective vehicle was given intraperitoneally 10 min before tapentadol.

In the first set of experiments involving intraperitoneal tapentadol administration, the minimal yohimbine dose (2.15 mg/kg i.p.) that produced complete antagonism of a maximally effective dose of the reference agonist reboxetine in both the low-intensity tail-flick test and the SNL model was used to compare the relative contribution of the NRI component to the effect of tapentadol in these two models (Schröder et al., 2010). In the second set of experiments involving intraperitoneal tapentadol administration in the low-intensity tail-flick test, the dose of yohimbine was further increased to a maximum of 4.64 mg/kg i.p. that did not produce confounding effects (i.e., caused by behavioral side effects) to ensure complete antagonism of the NRI component of tapentadol.

Drugs. Tapentadol (Grüenthal GmbH, Aachen, Germany) and naloxone and yohimbine (Sigma Chemie, Deisenhofen, Germany) were dissolved in saline (0.9% NaCl). The volume of administration was 5 ml/kg. The antagonists naloxone and yohimbine or the respective vehicle were given intraperitoneally 5 min (SNL) or 10 min (low-intensity tail-flick) before intravenous or intraperitoneal tapentadol treatment. Because mechanical hypersensitivity testing in the SNL model lasted approximately 5 min, whereas testing in the tail-flick assay was performed instantaneously, the administration time point of the antagonists relative to the agonists was adapted.
accordingly in the SNL model. Antagonist drug doses were carefully chosen to reach full antagonism of a maximally active dose of respective reference agonists (morphine, reboxetine) without confounding analgesic effect or behavioral side effects (Schröder et al., 2010). All doses refer to the respective salt form as indicated above.

Data Analysis. Data were analyzed by means of a one- or two-factor analysis of variance with or without repeated measures, depending on the experimental design, with a post hoc Bonferroni test. Significance of treatment, time, or treatment \times time interaction effects was analyzed by means of Wilks's \( \Lambda \) statistics. In case of a significant treatment effect, pairwise comparison was performed at the time of maximal effect by the Fisher least significant difference test. Results were considered statistically significant if \( P < 0.05 \).

Median effective dose (ED\(_{50}\)) values and 95% confidence intervals (CIs) were calculated by linear regression using the percentage of \( a \) from that relation one determines the combination dose pairs (\( a, b \)) that are calculated to give a specified level of effect (usually 50% of \( E_{\text{max}} \), although other effect levels can be used). This set of dose pairs constitutes the isobole for the selected effect level. This plot is almost always a line or curve having a negative slope in a rectangular coordinate plot of dose B against dose A. If each drug alone is capable of attaining the specified effect (e.g., 50% of \( E_{\text{max}} \)), then the intercepts of the graph denote the individual drug doses that give the half-maximal effect (see Fig. 1). If drug A alone does not reach the 50% effect level, then there is no intercept on the axis for any dose of drug A. The isobole may be interpreted as a visual that shows the diminution in the dose of drug B caused by the presence of the dose of drug A, and it is this diminution that accounts for its negative slope.

The exception to the negative slope is in that situation in which one of the drugs, say, drug A, lacks efficacy over some dose range. In this case there is no diminution in the needed dose of drug B; hence, in that case the isobole is a horizontal line (also shown in Fig. 1). The isobole has an historical use in defining unusual interactions (Loewe, 1953, 1957) and, in recent years, has witnessed a much expanded usage and application (Tallarida, 2001, 2007; Tallarida et al., 2003; Grabovsky and Tallarida, 2004; Braverman et al., 2008; Tallarida and Raffa, 2010). When experiments with actual combinations show that a dose pair below the isobole gives the specified effect, this means that lesser quantities were needed because of a synergistic interaction. In contrast, an experimental point above the isobole means an antagonistic interaction between the constituent drugs. Experimental points that lie on the isobole are the expected dose pairs under conditions of zero interaction and we refer to this case as an “additive interaction.” Details are given in several reviews (Tallarida, 2006, 2007; Tallarida and Raffa, 2010).

The theoretical basis of the isobole is the concept of dose equivalence for drugs A and B. Dose equivalence is determined from the individual dose-effect curves, i.e., a dose \( a \) of drug A will have a drug B-equivalent dose, \( b_{\text{eq}}(a) \). Thus, an actual dose \( b \) of drug B, when added to \( b_{\text{eq}}(a) \), is effectively the same as the ED\(_{50}\) of drug B: \( b + b_{\text{eq}}(a) = \text{ED}_{\text{50}} \). This mathematical relation defines the isobole and, in its most common form (when the relative potency is constant) the

![Fig. 1](http://jpet.aspetjournals.org/)

**Fig. 1.** The common isobole (which may be nonlinear or linear) is a decreasing curve (such as curve 1) when both drugs contribute based on their individual dose-effect curves. When both drugs achieve the desired effect (e.g., 50% level) then there are two intercepts representing the dose of drug A (denoted A) and the dose of drug B (denoted B) that individually give the specified effect level. When one of the drugs (e.g., drug A) does not contribute to the effect, then the isobole is horizontal (such as curve 2).
and 78% H2O), we calculate that the fraction of drug in solution (see Fig. 5), when adjusted for the brain composition (22% tissue in this, by using the brain concentration data (ng/g) for tapentadol (free drug) is 0.0335 which leads to a free concentration that is (0.0335/0.78) = 0.043 of that in the whole brain. Therefore, a factor of 0.04 in determining biophase concentration was used and this same value was used for calculating both the observed and expected (additive) concentrations and the corresponding fractional occupancies. A different factor would lead to a different biophase concentration and fractional receptor occupancy, but the results of this analysis, which compares two receptors in the brain for interactions, are independent of the precise biophase values, i.e., this comparative analysis is sufficiently robust as to not require exact values of the occupancies.

Interactions Viewed on the Effect Scale: an Alternative to Isobolographic Analysis. An alternative to isobolographic analysis uses drug combination data and derives the expected (additive) effect of the dose combination (a, b), i.e., an analysis on the effect scale. One might assume that the effect of the combination is a simple sum of the effects that each achieves alone, but that would be incorrect. For example, if the individual effects are, say, 70 and 55% of Emax, the addition of these percentages has no meaning. Thus, we used the concept of dose equivalence as follows: using symbols previously defined, we denote the effective dose of the combination as b + b(a), and this quantity is used in the dose-effect relation for drug B as its effective dose, thereby giving the additive effect of the combination. In the special case in which dose a alone lacks efficacy, then b(a) = 0, which means that this dose in the combination produces no change in the dose-effect relation of drug B.

Results

Interactions between the Two Mechanisms of Action Determined from the Effects of Tapentadol in Two Pain Models

One view of the interactions between the two mechanisms of action of tapentadol action is afforded from a comparison of the observed and (calculated) additive effect magnitudes. To this end, tapentadol was administered intravenously in varying doses as the sole agent as well as under conditions of yohimbine block (2.15 mg/kg i.p.) and naloxone block (1.0 mg/kg i.p.). The former case reveals tapentadol agonism caused by MOR stimulation, whereas the latter reveals agonism caused by NRI. Agonism in these two conditions was assessed in both an acute pain model (low-intensity tail-flick test) and a model of chronic mononeuropathic pain (SNL).

Low-Intensity Tail-Flick Test. A graded dose-effect relationship was found in this model, as shown in Fig. 2A. It is evident from these relationships that tapentadol’s MOR-mediated action was more potent than that caused by NRI in this test (Schröder et al., 2010). It is also seen (Fig. 2A) that the effect of NRI is not evident at tapentadol doses less than 4.64 mg/kg. Thus, in this low dose range the NRI component of action has no equivalent in terms of MOR agonism. It is therefore expected that, in this lower dose range, tapentadol’s antinociceptive dose effect will be the same as that caused by MOR agonism if the interaction is additive. It is seen, however, that the tapentadol effects are elevated above the MOR-mediated effects. This elevation is shown numerically in Table 1, which shows the effect (with 95% confidence limit [CL]) for both conditions in the tapentadol dose range ≤4.64 mg/kg. From the concept of dose equivalence the effects are expected to be the same for a simply additive interaction. However, they are seen to be different, and the significant difference at each dose is a manifestation of synergism between these two mechanisms of action.

SNL. The dose-effect relationships from this model are shown in Fig. 2B and reveal the interesting fact that tapentadol’s NRI-mediated action is more potent than the MOR component of action (Schröder et al., 2010). This stands in contrast to the situation revealed in the acute pain model described above, where naloxone produced a greater rightward shift of the tapentadol dose-response relationship as yohimbine. It is also seen that in the lower tapentadol dose range (< 4.64 mg/kg) the MOR component of action is not evident; therefore, the NRI component is expected to be the same as that of unblocked tapentadol if there is no interaction. However, there is a prominent elevation in effect levels, e.g., 54.3% versus 6.6% at the 2.15 mg/kg tapentadol dose (Table 1). It is further seen that even at the 4.64 mg/kg dose, where MOR agonism is virtually undetectable in the SNL model, the tapentadol effect is significantly above that caused by NRI agonism, a finding indicative of synergism. The effect values (with 95% CIs) are given in Table 1.

Interactions between the Two Components of Tapentadol Action Determined from Receptor Occupation-Effect Relations in the Low-Intensity Tail-Flick Test

Another view of the interactions between the two mechanisms of action of tapentadol is afforded from the use of the fractional occupation of each receptor type as determined from the values of its brain concentration in an analysis based on receptor occupation. In an additional set of experiments, tapentadol was administered intraperitoneally in varying doses as the sole agent as well as after prior administration of either naloxone (1.0 mg/kg i.p.) or yohimbine (4.64 mg/kg i.p.).

Tapentadol (alone) produced potent [ED50: 5.1 (4.4–5.8) mg/kg i.p.] dose- and time-dependent antinociception (treatment: \( F_{1,72} = 80.841, P < 0.001 \); time: \( F_{2,144} = 11.817, P < 0.001 \); interaction: \( F_{14,144} = 2.456, P < 0.001 \)). Full efficacy,
10 min after intraperitoneal administration, was reached at 31.6 mg/kg (Figs. 3 and 4). Naloxone significantly shifted the dose-response curve of tapentadol to the right by a factor of 5.2 \( [\text{ED}_{50}, 5.1 \text{ versus } 26.3 (21.7–31.2) \text{ mg/kg}; \text{treatment: } F_{7,69} = 25.184, P < 0.001; \text{time: } F_{2,138} = 0.113, P = 0.893; \text{interaction: } F_{14,138} = 1.475, P = 0.128] \) (Fig. 4). Statistical evaluation relates to the within-group effect of tapentadol, and differences between groups were assessed based on CI overlap (see Materials and Methods). Yohimbine significantly shifted the dose-response curve of tapentadol to the right by approximately a factor of 3 \( [\text{ED}_{50}, 5.1 \text{ versus } 15.2 (12.9–17.7) \text{ mg/kg}; \text{treatment: } F_{5,54} = 29.124, P < 0.001; \text{time: } F_{2,108} = 7.023, P < 0.001; \text{interaction: } F_{10,108} = 2.127, P = 0.028] \) (Fig. 4). These \( \text{ED}_{50} \) values are based on effects at 10 min after intraperitoneal tapentadol administration. Administration of vehicle or antagonists alone did not produce antinociceptive effects (see legend to Fig. 4).

**Brain Concentrations and Receptor Occupation of Tapentadol.** For use in the following analysis we show in Fig. 5 the relation between each intraperitoneal dose of tapentadol and the brain concentration determined 10 min after tapentadol administration. It is seen that the brain (and plasma) concentrations exhibit pronounced linearity up to doses of 46.4 mg/kg i.p. Generally, brain concentrations were approximately 4.5 times higher than in plasma. Effective plasma concentrations in humans are approximately 50 to 150 ng/ml,

**TABLE 1**

Effects of tapentadol and its dual component in two pain models

<table>
<thead>
<tr>
<th>Intravenous Tapentadol Dose</th>
<th>Low-Intensity Tail Flick</th>
<th>SNL</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/kg</td>
<td>Tapentadol Effect (%)</td>
<td>MOR Component Effect (%)</td>
</tr>
<tr>
<td>1.0</td>
<td>21.8 (4.6–29.0)</td>
<td>0</td>
</tr>
<tr>
<td>2.15</td>
<td>54.3 (44.4–64.2)</td>
<td>6.6 (0–15.8)</td>
</tr>
<tr>
<td>4.64</td>
<td>6.6 (0–15.8)</td>
<td>7.5 (22.8–52.2)</td>
</tr>
</tbody>
</table>

Effect values are presented as percentage of MPE (with 95% confidence limits) at 30 min after intravenous tapentadol administration. In each pain model the tapentadol effect is expected to equal that of the indicated component if the interaction is simply additive. These significantly greater effects indicate synergism. Data are from Schröder et al., 2010.
which is similar to the concentrations found in rat plasma at intraperitoneal doses of 1 to 4.64 mg/kg. Brain concentrations allow estimation of the biophase concentrations.

The fractional receptor occupation values were calculated from the biophase brain concentration values for each tapentadol dose and the previously determined dissociation constant of MOR (0.096 \text{H}^{11006} 0.009 \text{H}^{9262} M) and functional inhibition constant of NAT (0.48 \text{H}^{11006} 0.11 \text{H}^{9262} M) (Tzschentke et al., 2007).

Figure 6 shows the relation between receptor occupation and intraperitoneal tapentadol dose. The receptor occupation values for each dose were coupled to the effect (here determined from the low-intensity tail-flick test), thereby yielding the occupation-effect curves of Fig. 7. These graphs show the occupation-effect relation for MOR fractional occupation (using the effect data with yohimbine block) and the corresponding NAT fractional occupation that uses effects that accompany the naloxone block. For example, in Fig. 7A the six points shown are derived from the dose-effect data of Fig. 4. The doses have been transformed to MOR fractional occupancy and plotted with the observed effect and, from these, we note that the 50% effect occurs at MOR occupancy \text{H}^{11005} 0.92, the value that is used in constructing the subsequent isobole of additivity. Occupation-effect relations serve the same purpose as dose-effect relations for the detection of interactions. In this case, however, the interaction is not between two agonist drugs; it is, instead, between the two receptors occupied by the same drug. Just as dose equivalence is the basis of the common isobologram, it also follows that occupation equivalence is the basis of the isobologram in this case.

As seen in Fig. 8, the isobole of additivity (50% effect) is horizontal. This occurs because for all fractional occupancy values of the NAT that are less than 0.54 that occupied receptor yields no detectable effect in this low-intensity tail-flick test. (This is analogous to the situation in which one of the two drugs is devoid of efficacy, in which case the isobole...
of additivity is horizontal.) Thus, NAT occupation in the
range of 0 to 0.54 is negligible, and therefore the expected
additive isobole is horizontal at the 0.92 level (over the NAT
domain up to 0.54) of the expected MOR fractional occupation
for the half-maximal effect of the combined action (see also
Fig. 7A). The experimentally determined occupation pair for
this 50% effect, obtained from the tapentadol ED50 dose 5.1
mg/kg, is at a lower MOR occupancy value (0.67) with only
0.32 occupancy of NAT (X on Fig. 8), thereby showing syner-
gism because occupancy 0.32 yields no effect. In other words,
because this experimentally derived point is significantly
below the additive isobole a synergistic interaction between
these occupied receptors is indicated.

Discussion

Tapentadol exerts its antinociceptive action through two
mechanisms, MOR agonism and NRI, that have been well
documented (Tzschentke et al., 2006, 2007, 2009). The cur-
rent set of antinociceptive tests and accompanying analysis
further confirm this dual mechanism and provide a quanti-
tative analysis that shows that these two mechanisms inter-
act in a synergistic way. This is probably the first demon-
stration of a synergistic interaction between the occupied
receptors for a single compound with a dual mechanism of
action. This synergistic interaction was derived from our two
pronged analysis that included 1) an examination based on
occupation isoboles and 2) the observed and predicted effect
levels.

Viewed from the effect scale, the predicted (additive) effect
of a drug dose combination uses the concept of dose equiva-
lence, i.e., adding the drug B equivalent of drug A to the dose
of drug B, to calculate the combination effect when there is no
interaction. This same principle applies to isobolographic
analysis but that method derives its conclusion from compar-
isons of observed and expected doses (or receptor fractional
occupations) that give the specified effect magnitude. In this
study the isobolographic analysis used occupation isoboles
and is conceptually identical to that used in traditional iso-
lographic analysis with doses. When using occupation iso-
boles it is not dose equivalence; instead it is occupation equiv-
alence that underlies the analysis. All other aspects of the
traditional isobole apply to the occupation isobole in quanti-
tatively characterizing the interaction which, as applied to
tapentadol, is between the two occupied receptors (MOR and
NAT). The synergistic interaction between the two mecha-
nisms of action of tapentadol may well explain two remark-
able observations. Tapentadol has a 50-fold lower affinity for
the (rat) MOR than morphine ($K_i = 0.096$ versus $0.002 \mu M$),
yet tapentadol is only 2- to 3-fold less potent than morphine
across a variety of preclinical pain models (Tzschentke et al.,
2006), strongly suggesting that the NRI component of tapen-
tadol contributes to its analgesic effect, and that it does so in
a synergistic manner. Because the NRI activity of tapentadol
is also only relatively moderate ($K_i = 0.48 \mu M$ for rat synap-
tosomal uptake inhibition), a simple additive effect cannot
explain the potent analgesia observed for tapentadol. Thus,
through this synergistic interaction, two moderate pharma-
cological activities are sufficient to produce powerful analge-
 sia, along with reduced MOR-related and without relevant
NRI-related side effects.

The fact that the noradrenergic component contributes in a
synergistic way may also explain why tapentadol produces
potent analgesia in acute as well as in various chronic pain
states. In acute pain, monoaminergic compounds are gener-
ally relatively ineffective (see Tzschentke, 2002), and in

![Fig. 7. A, the occupation-effect relation for MOR fractional occupation
was obtained from dose-effect data of tapentadol in the presence of
yohimbine. The ED50 for MOR fractional occupation is 0.92 (correspond-
ing to dose 15.3 mg/kg) with 95% CLs (0.86–0.94). B, occupation-effect
relation for NAT (obtained with naloxone block) is plotted. This com-
ponent of tapentadol’s action is not evident for NAT fractional occupation
less than 0.54.](<image>)

![Fig. 8. Isobologram for 50% of the MPE based on receptor occupancy
showing synergism between the two components that contribute to tap-
entadol action in this test. Because NAT activity is not apparent up to
fractional occupancy 0.54, the additive isobole (solid line) is horizontal
(with 95% CLs shown as broken lines) and represents the occupation of
MOR for this effect level. The experimental occupation pair is shown (X)
with 95% CLs, and its position below the isobole indicates synergism.](<image>)
chronic pain, pure opioids, although still effective, are relatively less potent than in acute pain, necessitating dose escalation to obtain satisfactory analgesia. These high doses often cause intolerable opioid-typical side effects, limiting the usefulness of pure opioids in chronic pain (Portenoy, 1996; Kalso et al., 2004). It is noteworthy that whereas in acute pain models, the potency of tapentadol is (only) two to three times lower than that of morphine, in rat and mouse models of chronic (mononeuropathic and polyneuropathic) pain, the potency difference between tapentadol and morphine is even smaller, or tapentadol is even more potent than morphine (Tzschenkte et al., 2009; Christoph et al., 2010; Schröder et al., 2010). This is probably related to the fact that noradrenergic mechanisms play a more relevant role in chronic in as in acute pain states (Fishbain, 2000; Tzschenkte et al., 2007; Schröder et al., 2010), such that the (synergistic) contribution of this mechanism is even more pronounced in chronic pain, leading to an even more pronounced potency advantage over pure opioids (relative to the MOR affinity).

A mechanistic/anatomical basis for this synergistic interaction may lie in the intricate interplay between the opioid system and monoaminergic systems (in particular the descending inhibitory noradrenergic system). Opioids act at several levels of the pain transmitting system. At the spinal level, opioids reduce the transmission of the pain signal from the primary afferents to the fibers of the spinothalamic tract via presynaptic and postsynaptic mechanisms (Millan, 1999). At the supraspinal level, in addition to various other effects, opioids activate the descending inhibitory pathways to the spinal cord. Within these pathways, noradrenaline is an important transmitter (Millan, 2002). Thus, a NRI mechanism of action contributes to analgesia by increasing noradrenergic activity at the spinal level by augmenting the influence of the descending inhibitory projection. By combining MOR and NRI mechanisms of action, analgesic potency is enhanced, not only through a summation of the individual effects at the supraspinal and the spinal level, but also through a mutual interaction of supraspinal and spinal effects. The effect of the opioid-induced supraspinal activation of the descending inhibitory noradrenergic pathways is further enhanced through the action of the NRI component at the spinal level. In other words, the MOR-agonistic component increases spinal levels of noradrenaline that in turn acts on spinal α2 adrenoceptors, and the NRI component also blocks the reuptake of this additionally released noradrenaline. Previously, it was shown that noradrenaline reuptake inhibitors are antinociceptive on their own and also potentiate the analgesic effect of both systemic and intrathecal morphine when administered spinally (Hwang and Wilcox, 1987). Furthermore, the complex supraspinal-spinal interaction between MOR and α2 adrenoceptors as described above was shown to underlie the antinociceptive synergism obtained with concurrent intrathecal and intracerebroventricular morphine administration in the mouse tail-flick test (Wigdor and Wilcox, 1987). Likewise, we were able to demonstrate a pronounced supraspinal-spinal synergism for tapentadol in heat hyperalgesia in a mouse model of streptozotocin-induced diabetic polyneuropathy and showed that this site-specific synergism is mediated predominantly at the spinal level (T. Christoph, unpublished work).

Because of this intricate interaction and mutual augmentation of the individual effects, relatively moderate pharma
cological activities are sufficient for both mechanisms of action of tapentadol to achieve a powerful analgesic effect. This, in turn, translates into a broad efficacy profile and clearly improved clinical tolerability (Hale et al., 2009; Hartrick et al., 2009; Hartrick, 2009).

In conclusion, a quantitative analysis based on additive isoboles of occupation and/or additive effects can be applied to study the interaction between two mechanisms of action located within a single molecule. The data presented here for tapentadol show that these mechanisms interact in a highly synergistic way. This may well explain why tapentadol is only 2–3-fold less potent than morphine across a variety of preclinical pain models despite a 50-fold lower affinity for the MOR. This is probably the first demonstration of a synergistic interaction between the occupied receptors for a single compound with a dual mechanism of action.

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Authorship Contributions

Participated in research design: Schröder, Tzschenkte, Terlinden, De Vry, Jahnel, Christoph, and Tallardia.

Conducted experiments: Schröder and Christoph.

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References


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Correction to “Synergistic Interaction between the Two Mechanisms of Action of Tapentadol in Analgesia”

In the above article [Schröder W, Tzschentke TM, Terlinden R, De Vry J, Jahnel T, Christoph T, and Tallarida RJ (2011) J Pharmacol Exp Ther 337:312–320], acknowledgment of funding from the National Institutes of Health National Institute on Drug Abuse [Grant 2P30 DAO13429] was omitted.

The authors regret this error and any inconvenience it may have caused.