Antidepressant-like activity of selective serotonin reuptake inhibitors combined with a NK1 receptor antagonist in the mouse forced swimming test

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Abstract

Substance P antagonists of the neurokinin-1 receptor type (NK1) have growing interest as new antidepressant therapies. It has been postulated that these drugs exert this putative therapeutic effect without direct interactions with serotonin (5-HT) neurons. In line with this assumption, previous intracerebral in vivo microdialysis experiments provided evidence that the NK1 receptor antagonists did not change basal cortical 5-HT levels. However, we found that increases in cortical 5-HT overflow caused by systemic injection of the selective serotonin reuptake inhibitor (SSRI), paroxetine was higher in freely moving (C57BL/6x129sv) NK1−/− mutants than in wild-type NK1+/+ mice [17]. More recently, a pharmacological study has led to a similar conclusion since GR205171, a NK1 receptor antagonist, potentiated paroxetine-induced increases in cortical 5-HT dialysate following its acute systemic or intra-raphe administration to wild-type mice [25]. In the present study, we tested whether an acute combination of SSRI and NK1 receptor antagonist could display antidepressant-like activity using the forced swimming test in Swiss mice. We found that a single systemic dose of GR205171 (10 and 30 mg/kg, i.p.) had no effect by itself. However, it selectively potentiated the antidepressant-like activity of subactive doses of two serotonergic antidepressant drugs, citalopram and paroxetine (without psychomotor stimulant activity), but not that of noradrenaline reuptake inhibitor, desipramine. In agreement with neurochemical data, the present study confirms that co-administration of a NK1 receptor antagonist with an antidepressant drug such as a SSRI may have a therapeutic potential to improve the treatment of major depressive episodes in human compared to SSRI alone.

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Keywords: Forced swimming test; Mouse; NK1 receptor antagonist; Selective serotonin reuptake inhibitor; Substance P

1. Introduction

To the present knowledge, antidepressant drugs used in the treatment of major depressive disorders are believed to act on the central monoaminergic systems mainly serotonin (5-hydroxytryptamine, 5-HT) and noradrenaline (NA) synap-
Substance P (SP), a member of tachykinin family, is widely distributed within the brain and exerts its biological effects mainly through the activation of the G protein-coupled neuropeptide I (NK1) receptor [51]. During the past 10 years, clinical trials carried out in depressed patients revealed a putative new class of antidepressant drugs known as the NK1 receptor antagonists. Initial phase II studies of the NK1 receptor antagonists MK689, L759274 and CP122721 have reported a higher rate of symptoms remission than that of paroxetine, fluoxetine or placebo [10,31,32]. However, these compounds exhibit the same delay of therapeutic effects as SSRIs (for review, see [36]). A recent clinical study has compared the effects of a NK1 receptor antagonist alone and citalopram on anxiety symptoms in social phobia [18] and demonstrated that short-term administration of either GR205171 or citalopram similarly alleviated social anxiety. Despite these encouraging results, a progressive decreased antidepressant-like activity of drugs after their acute administration [13,57] was observed. This lack of interest is most likely due to the fact that approximately half of the antidepressant clinical trials performed with NK1 receptor antagonists failed to differentiate these new drugs from placebo or comparators [29,39,42].

Although the antidepressant properties of NK1 receptor antagonists were first attributed to a new mechanism, without interfering with central monoamine systems [31], various preclinical approaches have revealed that NK1 receptor antagonists can modulate both 5-HT and NA neurotransmission in the brain (for reviews, see [1,4,19,24]). For example, it was reported that the genetic inactivation of NK1 receptors causes a functional desensitisation of 5-HT1A autoreceptors and alpha-2 adrenoceptors [17,28,50] as observed with SSRIs and NRIs [33,45]. As a direct consequence, microdialysis experiments have demonstrated that the increase in cortical extracellular 5-HT and NA levels induced by paroxetine and desipramine respectively, were higher in NK1−/− KO mice than in their wild-type littersmates [17,28]. Likewise, paroxetine-induced increase in cortical [5-HT]ext was potentiated in wild-type mice receiving a single or repeated administration (for 3 weeks) of the NK1 receptor antagonist, GR205171 [22,25] suggesting that NK1 receptor antagonism may strengthen the antidepressant-like activity of SSRIs. This, hypothesis postulates that a high levels of [5-HT]ext at serotonergic nerve terminals, would predict a high degree of antidepressant effect by stimulating post-synaptic 5-HT receptor sub-types in brain regions involved in mood disorders. Interestingly, many studies demonstrated the antidepressant-like effect of various NK1 receptor antagonists given alone in both the forced swimming test [13,57] and the tail suspension test [55]. However, to our knowledge, no combination studies have been performed using co-administration of NK1 receptor antagonist and antidepressant drugs.

Thus, the present study was aimed to evaluate the antidepressant-like effects of paroxetine, citalopram and the NRI desipramine in association with a non peptidic, selective and brain penetrant NK1 receptor antagonist GR205171 [46], using the mouse forced swimming test (FST). This behavioural test is one of the most widely used preclinical paradigms for predicting antidepressant-like activity of drugs after their acute administration [41] alone or in combination.

2. Material and methods

2.1. Animals

Male Swiss mice (Centre d’Élevage Janvier, Le Genest, France) 4 weeks old and weighing 20 ± 2 g at the treatment day were housed in groups of 18 per cage (40 cm × 28 cm × 17 cm) in the standard conditions of the animal room (21 ± 1 °C, standard light/dark cycle light on at 7:00 h, off at 19:00 h) with free access to food and water for a period of 1 week before use. Each experimental group consisted of naïve randomly grouped mice of the same weight, which were used only once (evaluation of locomotor activity or forced swimming test). All experiments were performed within the guidelines of the French Ministry of Agriculture for experiments with laboratory animals (law 87 848).

2.2. Drugs and treatment

GR205171 and paroxetine hydrochloride were generous gifts from GlaxoSmithKline laboratory (Harlow, UK), and citalopram hydrobromide from Lundbeck (Copenhagen, Denmark). Range doses of SSRIs (4–16 mg/kg) and that of desipramine HCl (2–8 mg/kg) (Sigma, France) were dissolved in NaCl 0.9% and administered intraperitoneally (i.p.) (25 ml/kg) 30 min before testing. GR205171 (10 and 30 mg/kg) was dissolved in NaCl 0.9% and injected i.p. (25 ml/kg) 15 min before behavioural test. Only subactive doses of antidepressant drugs (citalopram, desipramine and paroxetine) were co-administered with GR205171; these doses were defined the day of test. Doses of GR205171 were chosen according to our previous results: we have already demonstrated that this compound administered by an intraperitoneal route at the dose of 30 mg/kg in mice, was able to modify the central 5-HT neurotransmission [25], and reversed the effects of centrally administered substance P [23].

2.3. Behavioural tests

2.3.1. Measurement of locomotor activity in mice [5]

Animals (nine mice per group) were kept in the darkened test-room at least 1 h before the test for habituation. After injection (pretreatment and/or treatment), mice were replaced in their holding cages for the required injection-test interval, and then individually transferred to the actimeter for the 10 min test. These animals were different from those used in the forced swimming test. The spontaneous activity of naïve animals was recorded using a photoelectric actimeter (Osys, Laval France). This actimeter consists of a stainless steel apparatus containing transparent cages in which the animals horizontal activity is measured by light beams connected to a photo-electric cell. Results are expressed as the number of light beams broken during the 10 min test period (mean ± S.E.M.) for each group.

2.3.2. Measurement of immobility time in the forced swimming test [41]

The forced swimming test employed was essentially similar to that described elsewhere [40]. Briefly, mice were dropped individually into glass cylinders (height: 25 cm; diameter: 10 cm) containing 10 cm water, maintained at 25 ± 1 °C, and remained there for 6 min. A mouse was judged to be immobile when it floated in an upright position and made only small movements to keep its head above water. Six mice were tested simultaneously, and the time of immobility was recorded during the last 4 min of the 6 min testing period, thus after 2 min of habituation. The test was performed by the same well-trained experimenters, blind to the treatment administered. Results are expressed as the immobility time during the 240-s test period (mean ± S.E.M.) for the 10 mice tested in each group.

2.4. Statistical analyses

Statistical analyses were performed using the computer software Sigmasstat (Systat software, Erkrath, Germany). A two-way ANOVA on the immobil-
Fig. 1. Interaction of subactive doses of citalopram and GR205171 (10 and 30 mg/kg) in mice FST. All groups consisted of 10 mice. Results are expressed as mean immobility time ± S.E.M. † indicate a significant difference with control group receiving the same treatment (NaCl or GR205171). Asterisks show a significant difference compared to group receiving same dose of antidepressant.

† †† ††† p < 0.01; † † p < 0.05; † p < 0.001.

Fig. 2. Interaction of subactive doses of paroxetine and GR205171 (10 and 30 mg/kg) in mice FST. All groups consisted of 10 mice. Results are expressed as mean immobility time ± S.E.M. † indicate a significant difference with control group receiving the same treatment (NaCl or GR205171). Asterisks show a significant difference compared to group receiving same dose of antidepressant.

† p < 0.05; † † p < 0.01; † †† p < 0.001; † † † p < 0.001.

Fig. 3. Interaction of subactive doses of desipramine and GR205171 (10 and 30 mg/kg) in mice FST. All groups consisted of 10 mice. Results are expressed as mean immobility time ± S.E.M. † indicate a significant difference with control group receiving the same treatment (NaCl or GR205171). † † p < 0.01.

3.1. Effect of combined administration of GR205171 and sub-active doses of citalopram in the mouse FST

The two-way ANOVA (pre-treatment × treatment) performed revealed significant main effects of pre-treatment (saline or citalopram: $F_{2,81} = 11.56; p < 0.001$), treatment (saline or GR205171: $F_{2,81} = 7.75; p < 0.001$) and an interaction between the two factors ($F_{4,81} = 2.92; p < 0.05$). Citalopram given alone induced a significant antidepressant-like effect at 16 mg/kg ($p < 0.01$), but not at lower doses (4 and 8 mg/kg) as compared to the vehicle-treated control group (Fig. 1).

The lowest dose of GR205171 (10 mg/kg) did not modify the immobility time in mice when combined with inactive doses of the SSRI.

However, the highest dose of GR205171 (30 mg/kg) co-administered with inactive doses of citalopram induced an antidepressant-like effect (in comparison with the corresponding dose of GR205171 given alone ($p < 0.001$). The NK1 receptor antagonist also significantly enhanced the antidepressant-like effect of citalopram alone 4 and 8 mg/kg ($p < 0.01$ and $p < 0.05$, respectively).

3.1.2. Effect of combined administration of GR205171 and subactive doses of paroxetine in the mouse FST

The two-way ANOVA performed revealed significant main effects of pre-treatment (saline or paroxetine: $F_{2,81} = 15.18; p < 0.001$) and treatment (saline or GR205171: $F_{2,81} = 3.88; p < 0.05$), but no interaction between the two factors ($F_{4,81} = 0.891; p = 0.47$). Paroxetine given alone induced a significant antidepressant-like effect at 16 mg/kg ($p < 0.001$), but not at lower doses (4 and 8 mg/kg) as compared to the vehicle-treated control group (Fig. 2). The co-administration of GR205171 (at both doses) and paroxetine (4 and 8 mg/kg) induced an antidepressant-like effect when compared to the corresponding doses of GR205171 alone. Interestingly, the NK1 receptor antagonist (10 and 30 mg/kg) significantly enhanced...
the antidepressant-like effect of paroxetine only when the SSRI was given at the dose of 8 mg/kg ($p < 0.05$ in comparison to the corresponding doses of paroxetine alone).

3.1.3. Effect of combined administration of GR205171 and subactive doses of desipramine in the mouse FST

The two-way ANOVA performed did not reveal significant effects of pretreatment (saline or desipramine; $F_{2,81} = 2.157; p = 0.12$), treatment (saline or GR205171; $F_{2,81} = 1.77; p = 0.18$) nor interaction between these two factors ($F_{4,81} = 0.86; p = 0.49$) suggesting that GR205171 did not potentiate the antidepressant-like effect of subactive doses of desipramine (2 and 4 mg/kg) in the mouse FST. Desipramine given alone induced a significant antidepressant-like effect at 8 mg/kg only ($p < 0.001$) (Fig. 3).

3.2. Measurement of locomotor activity

3.2.1. Effect of GR205171 on spontaneous locomotor activity of antidepressant drugs

GR205171 (10 and 30 mg/kg) was tested alone or in combination with various antidepressant drugs in the locomotor activity apparatus in order to test whether or not the variation in the immobility time evaluated in the mouse FST could be linked to a modification of the antidepressant-like effect of drugs rather than a modification of the spontaneous locomotor activity.

3.2.2. GR205171 given alone

The results showed that GR205171 did not induce any psychostimulant effects at the doses employed (Table 1). At the opposite, when given alone, GR205171 (10 mg/kg) significantly decreased the locomotor activity in mice ($F_{2,24} = 2.73; p < 0.05$).

3.2.3. Citalopram

The two-way ANOVA revealed significant effects of both pre-treatment ($F_{2,72} = 8.59; p < 0.001$) and treatment ($F_{2,72} = 7.02; p < 0.01$) factors, but no interaction between the two factors ($F_{4,72} = 1.44; p = 0.23$). Thus [Cital 8 + NaCl], [Cital 4 + GR10] and [Cital 8 + GR10] induced a psychostimulant effect in comparison with their own control ([NaCl + NaCl] and [NaCl + GR10], respectively). However, although these data would represent a confounding factor in the interpretation of our results, we have reported in the present study that the abovementioned combinations did not produce antidepressant-like effects. Conversely, at the highest dose tested, GR205171 decreased the locomotor activity when co-administered with citalopram 4 mg/kg ($p < 0.05$) suggesting therefore that the enhancement of the mobility time of mice obtained in the FST, following combined administration, was only linked to an enhancement of antidepressant-like activity of the SSRI citalopram.

3.2.4. Paroxetine

The two-way ANOVA performed revealed significant effects of both pre-treatment ($F_{2,72} = 3.57; p < 0.05$) and treatment ($F_{2,72} = 5.64; p < 0.01$) factors, but no interaction between the two factors ($F_{4,72} = 1.56; p = 0.19$). When combined with paroxetine 4 mg/kg, GR205171 (10 mg/kg) increased the locomotor activity ($p < 0.05$), and the effect of treatment revealed a significant sedative effect of [Prx 4 + GR30], when compared to [Prx 4 + NaCl] ($p < 0.05$). The enhancement of the antidepressant-like activity of paroxetine 8 mg/kg by GR205171 was not associated with changes in the spontaneous locomotor activity.

3.2.5. Desipramine

The two-way ANOVA performed revealed significant effects of both pre-treatment ($F_{2,72} = 10.33; p < 0.001$) and treatment ($F_{2,72} = 5.13; p < 0.01$) factors, but no interaction between the two factors ($F_{4,72} = 1.56; p = 0.50$). Thus, desipramine 4 mg/kg induced a sedative effect when given alone ($p < 0.01$). The locomotor activity of mice was not decreased further to administration of GR205171 (in combination with desipramine). The absence of enhancement of antidepressant-like activity of desipramine could then not be linked to a sedative effect of the NK1 receptor antagonist.

Table 1

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>Doses (mg/kg)</th>
<th>Pre-treatment alone</th>
<th>Pre-treatment + GR205171 (10)</th>
<th>Pre-treatment + GR205171 (30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (NaCl)</td>
<td>185.8 ± 13.8</td>
<td>139.8 ± 12.8*</td>
<td>153.2 ± 9.7</td>
<td></td>
</tr>
<tr>
<td>SSRI Citalopram</td>
<td>4</td>
<td>197.9 ± 21.2</td>
<td>203.7 ± 11.6</td>
<td>151.2 ± 11.3*</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>251.9 ± 12.8</td>
<td>209.7 ± 24.4</td>
<td>182.1 ± 21.4</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>4</td>
<td>202.3 ± 18.4</td>
<td>208.0 ± 25.7</td>
<td>133.0 ± 15.2*</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>225.0 ± 16.1</td>
<td>194.3 ± 20.6</td>
<td>177.9 ± 24.3</td>
</tr>
<tr>
<td>NRI Desipramine</td>
<td>2</td>
<td>159.4 ± 13.1</td>
<td>134.3 ± 12.1</td>
<td>119.7 ± 10.9</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>121.6 ± 9.9</td>
<td>102.1 ± 9.7</td>
<td>116.1 ± 18.0</td>
</tr>
</tbody>
</table>

Effect of co-administration of antidepressants and GR205171 on spontaneous locomotor activity. All groups consist of nine mice. Data are expressed as numbers of light beams broken during the 10-min testing period. All the statistical analyses were calculated by Newman–Keuls test following significant ANOVA. Asterisks indicate difference between animals receiving (pre-treatment + GR205171) and animals receiving (pre-treatment alone) (*$p < 0.05$). Data in bold indicate difference between animals receiving (Antidepressant ± GR205171) and animals receiving (NaCl ± GR205171) ($p < 0.05$).
4. Discussion

The present study was carried out to evaluate the antidepressant-like activity of the conventional antidepressant drugs, SSRIs and NRIs, when combined with the NK1 receptor antagonist GR205171. Our results provide evidence that the association of both paroxetine and citalopram, but not desipramine, with GR205171 produced a significant antidepressant-like effect in the mouse FST, whereas, each pharmacological agent given separately had no activity. The potentiated efficacy of this combination suggests that the blockade of two distinct targets, the 5-HT transporter and the NK1 receptor, may improve the treatment of depressive episodes in humans.

4.1. NK1 receptor antagonists alone

A dysregulation of the SP neurotransmission in limbic structures has been proposed to play a role in stress-related paradigms and disorders. Accordingly, SP and its preferred NK1 receptors have been identified within the regions of CNS that are traditionally associated with stress (DRN, LC, frontal cortex, hippocampus, amygdala) (for review, see [1]). Acute or chronic stressors are also known to increase SP content in these brain regions [15,31,54]. Moreover, in guinea-pigs, central infusion of SP agonists causes long lasting audible stress vocalizations which can be abolished by pretreatment with NK1 receptor antagonists or antidepressant drugs such as imipramine or fluoxetine [31]. Together, these preclinical data raise interesting questions regarding the putative role of SP and related-NK1 receptors in the pathophysiology of depression and its interaction with central monoaminergic systems. Here it was shown that GR205171 (10 and 30 mg/kg, i.p.) per se, did not produce antidepressant-like activity in the mouse FST (Figs. 1–3). Even if GR205171 alone tended to decrease the spontaneous locomotor activity (Table 1), the lack of antidepressant-like effect could probably not be related to a sedative activity since it was demonstrated that many antidepressant drugs with sedative effects (such as imipramine, desipramine and clonidine) exhibit an antidepressant-like activity in the mouse FST [14,27]. Contrasting with the present findings, it was previously shown that a single administration of various NK1 receptor antagonists was reported to reduce the time of immobility in mice ([57]; GR205171 30 mg/kg, i.p.), rats ([13]; CP96345 5 mg/kg, i.p.) and gerbils ([55]; MK869, L742694 and L733060 10 mg/kg, p.o., CP99994 and CP122721 30 mg/kg, p.o.) submitted to FST. Species differences need to be considered, in the pharmacology of the antagonists, given that many of the compounds have reduced affinity for the rodent NK1 receptor, and thus often require high doses to observe an effect [46,47]. Discrepancies may also be attributed to methodological considerations such as distinct time interval between drug administration and the test itself (30 and 15 min), the level of stress between species or the use of different strains of mice since genotype is an important factor determining sensitivity to antidepressant drugs in behavioural tests [7,14,44]. For example, Swiss mice are the most sensitive strain to detect antidepressant-like activity of SSRI or SNRI in the FST. Finally, it can be assumed that in our experimental conditions, a single administration of GR205171 is not sufficient to induce an antidepressant-like effect. Nevertheless, the lack of antidepressant-like activity of GR205171 reported here is consistent with in vivo and in vitro data showing that an acute administration of NK1 receptor antagonist did not modify the spontaneous firing of DRN 5-HT neurons and the basal extracellular concentration of 5-HT ([5-HT]ext) in the frontal cortex of mice [22,25,57] or rats [12,26,34,38]. Thus, although the behavioural effects of NK1 receptor antagonists remain somewhat equivocal, there is now a large body of evidence suggesting that acute NK1 receptor antagonism does not modify 5-HT neurotransmission within brain regions involved in mood disorders.

4.2. NK1 receptor antagonist in combination

4.2.1. With selective serotonin reuptake inhibitor

It was shown here that a single intraperitoneal administration of the SSRIs citalopram and paroxetine (16 mg/kg), decreased the time of immobility in the mouse FST as compared to the control group receiving vehicle alone (Figs. 1 and 2). Surprisingly, lower doses have failed to produce antidepressant-like effects and these results diverge from previous dose-response studies performed in the mouse FST [14]. Such differences likely result from different factors (housing conditions, testing procedures) known to alter the sensitivity to SSRIs [6,40]. Nevertheless, the main finding of the present study is the significant reduction of time of immobility when subactive doses of citalopram (4 and 8 mg/kg) and GR205171 (30 mg/kg) were combined as compared to the corresponding groups of mice treated either with citalopram alone (p<0.01 and p<0.05, respectively) or GR205171 (30 mg/kg) alone (p<0.001 and p<0.01, respectively) (Fig. 1). Similarly, a significant reduction of the time of immobility was obtained from the association of the subactive dose of paroxetine (8 mg/kg) with GR205171 (10 and 30 mg/kg) as compared to the corresponding groups of mice treated either with paroxetine alone (p<0.05 for each dose of GR205171) or GR205171 alone (p<0.05 and p<0.001, respectively) (Fig. 2). It is noteworthy that the combination of SSRIs and GR205171 did not produce psychomotor stimulant effects as compared to SSRI alone (Table 1), suggesting that the effects observed in the mouse FST are specifically related to antidepressant-like activity. The neurochemical changes that could underlie these behavioural effects remain unclear and likely complex. Nevertheless, since an increase in 5-HT availability at nerve terminals is essential for antidepressant-like efficacy, we could infer that the combination of SSRIs and NK1 receptor antagonist have produced an enhancement of 5-HT neurotransmission in the brain regions involved in mood disorders. In line with this assumption, promising results were initially described by using a microdialysis approach in freely moving mice [25].

An important question raised by these microdialysis and behavioural results concerns the mechanism of action of NK1 receptor antagonists and whether these pharmacological agents act via a common molecular target similar to SSRIs? We previously demonstrated that NK1 receptor antagonists act by stimulating the release of 5-HT at nerve terminals rather than
inhibiting its reuptake [25]. In agreement, recent in vitro observations using human neocortical synaptosomes indicated that the selective blockade of NK1 receptors did not affect basal 5-HT uptake or the inhibition of 5-HT uptake induced by the SSRI fluvoxamine [35] suggesting that NK1 receptor antagonists do not interfere with the 5-HT transporter protein. Reverse microdialysis experiments with local intra-raphe injection of NK1 receptor antagonist suggested that the main interaction site between Substance P-ergic and serotonergic systems is located in the dorsal raphe nucleus (DRN) indicating that serotonin pathways are playing a critical role in the potentiation of the antidepressant-like activity. These results strongly suggest that co-administration of SSRI and a NK1 receptor antagonist can enhance 5-HT neurotransmission presumably through a lower inhibitory feedback control of the serotonergic neurons by 5-HT1A autoreceptors [24,25].

So far, two mechanisms can be proposed: NK1 receptor antagonists may reduce SSRI-induced activation of the negative feedback on 5-HT system. Otherwise, an effective clearance of 5-HT from the synapse may mask the increase in 5-HT release induced by NK1 receptor antagonists alone. In these conditions, SSRIs might unveil the activity of NK1 receptor antagonists by preventing the 5-HT reuptake process.

4.2.2. With selective noradrenalin reuptake inhibitor

In agreement with our previous dose-response study performed in Swiss mice [14], it was shown here that a single administration of the SNRI, desipramine at the dose of 8 mg/kg, i.p., decreased the time of immobility in the mouse FST as compared to the control group receiving vehicle alone (Fig. 3). In addition, GR205171 (10 and 30 mg/kg, i.p.) failed to potentiate the antidepressant-like activity of subactive doses (2 and 4 mg/kg, i.p.) of desipramine (Fig. 3). Although this effect could be related to a sedative activity of GR205171, we have shown that addition of the NK1 receptor antagonist did not modify desipramine-induced decrease in spontaneous locomotor activity (Table 1). It would be a relevant interest to determine whether or not a pharmacological inactivation of NK1 receptors could enhance the antidepressant-like activity of an active dose of desipramine. To our knowledge, no experiments have examined the neurochemical and behavioural changes produced by the association of SNRIs and NK1 receptor antagonists. Therefore, although previous observations have reported that the basal cortical efflux of noradrenaline increased two to four-fold in NK1−/− mice compared to NK1+/+ mice, the net increase in noradrenaline efflux in the cerebral cortex following injection of desipramine did not differ in NK1−/− and NK1+/+ genotype mice [28].

Taken together, our results interestingly suggest that a change in basal 5-HT neurotransmission is probably necessary to obtain an augmentation effect of NK1 receptor antagonist on activity of antidepressant drugs.

5. Conclusion

In conclusion, the present behavioural data in response to the co-administration of SSRIs with a NK1 receptor antagonist paralleled changes measured in cortical [5-HT]ext [24]. It is interesting to note that small molecules with dual NK1 antagonism and serotonin reuptake inhibition properties (NK1/SSRI) exhibit a robust neurochemical and antidepressant-like activities in animal models [48,49]. This new potentiating antidepressant strategy should now arouse psychiatrists towards clinical trials to determine the extend to which this chronic combination would display advantages over existing therapies with conventional antidepressant drugs, particularly to reduce the long delay of action and resistant rate of depressed patients to the SSRIs. It is also interesting to note that many augmentation strategies have been proposed to enhance the effects of currently prescribed antidepressant drugs. The most commonly used augmenting agents (lithium and buspirone; for review, see [30]) have also been demonstrating as being augmenting agents in the mouse FST [9,43] and in intracerebral microdialysis studies in rodents [8,11,20,21]. Consequently, these findings suggest that correlation between microdialysis and FST data had a predictive value on clinical results.

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