Pharmacology Biochemistry and Behavior, Vol. 63, No. 2, pp. 333–338, 1999

0091-3057/99/$–see front matter

ELSEVIER

PII S0091-3057(98)00245-7

Onset of the Effects of the 5-HT_{1A} Antagonist, WAY-100635, Alone, and in Combination With Paroxetine, on Olfactory Bulbectomy and 8-OH-DPAT–Induced Changes in the Rat

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Received 15 August 1998; Revised 15 December 1998; Accepted 15 December 1998

CRYAN, J. F., C. MCGRATH, B. E. LEONARD AND T. R. NORMAN. *Onset of the effects of the 5-HT_{1A} antagonist, WAY-100635, alone and in combination with paroxetine, on olfactory bulbectomy and 8-OH-DPAT–induced changes in the rat.* PHARMACOL BIOCHEM BEHAV **63**(2) 333–338, 1999.—5-HT_{1A} receptor antagonists have recently been shown to accelerate the efects of some antidepressant drugs in clinical trials. In this study we investigate the effects of combining a full antagonist at the 5-HT_{1A} receptor, WAY 100635 (0.2 mg/kg, SC) with the selective serotonin reuptake inhibitor (SSRI) paroxetine (5 mg/kg, IP) in the olfactory bulbectomized (OB) rat, an animal model of chronic (but not acute) antidepressant activity. Ambulation scores were measured in the open-field apparatus, following 3, 7, and 14 days of treatment. Further to the OB study, we simultaneously studied adaptive changes in 5-HT_{1A} receptor function, utilizing alterations in the hypothermic response to the 5-HT_{1A} receptor agonist 8-OH-DPAT. Paroxetine, in combination with WAY 100635, attenuated the hypothermic effects of 8-OH-DPAT as early as 3 days, with a full reversal evident following 7 days, whereas paroxetine, although attenuating the hypothermic effects in OB group by day 7, only reversed it fully after 14 days. Paroxetine alone and in combination with the antagonist reversed the olfactory bulbectomy-induced hyperactivity in the open field following 14 days of treatment only, this being the normal time of an "antidepressant" response in this model. However, there was no significant attenuation at any of the earlier time points. This further demonstrates that the reversal of this aspect of the olfactory bulbectomy-induced behavioral syndrome is insensitive to the potential faster onset of antidepressant action induced by 5-HT_{1A} receptor antagonists. Nonetheless, WAY 100635, unlike previous studies with pindolol, did not interfere with the effects of the antidepressant in the model. The ability of the combination group to attenuate the hypothermic effects of 8-OH-DPAT faster than paroxetine alone, further emphasizes the role of the 5-HT_{1A} receptor in the mechanism of action of antidepressants, and as a target for the development of faster acting antidepressants. © 1999 Elsevier Science Inc.

Olfactory bulbectomy Antidepressant Onset of action 8-OH-DPAT–induced hypothermia
5-HT_{1A} receptor Paroxetine WAY 100635

THE emphasis on the role of 5-HT in the pathogenesis of depression and other affective disorders has grown substantially over the past 30 years, especially with the advent of the selective serotonin reuptake inhibitors (SSRIs) as drugs of choice in the pharmacotherapy of depression (30). However, despite the many advantages the SSRIs and other newer antidepressants have over their tricyclic predecessors, they share with them a similar delay in their onset of action (41,48). Microdi-

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alysis and electrophysiological studies in rodents have implicated adaptations to the inhibitory somatodendritic 5-HT_{1A} receptor as playing a crucial role in this delay [see (4)]. It has been shown that following repeated administration of SSRIs and other antidepressants, a functional desensitization of this 5-HT_{1A} receptors occurs (7), which results in the release of inhibition of firing, mediated by 5-HT_{1A} receptors and the recovery of raphe neurons, while 5-HT reuptake blockade is maintained. The net effect being an increase in available extracellular 5-HT (1,18,25,26). This effect has also been shown to be equally achievable following acute treatment with antidepressants concomitantly with a 5-HT_{1A} receptor antagonist (2,15,16,19,23,24,35,40,45,47). Therefore, theoretically, if an increased extracellular 5-HT is the crux of an earlier onset of action, then combinations of 5-HT_{1A} antagonists and antidepressants should be efficacious in reducing the lag time prior to antidepressant response (4). Although still controversial, the use of the β-adrenoceptor/5-HT_{1A} receptor antagonist pindolol as an adjunct to conventional antidepressant treatment has stimulated much interest with claims of its ability to decrease the latency period before the therapeutic effect appears (3,5,8,34,42,50,53). It should be emphasized also that not all investigators have confirmed these findings (6,14). Although still primarily experimental, this strategy has helped to substantiate the 5-HT theory of depression, and may enable faster-acting antidepressants to be designed.

Various animal models have been developed to detect antidepressant activity of compounds and to simulate the biological changes seen in the depressed patient [see (31)]. Such models have not only been used to screen drugs for potential antidepressant activity but have also helped in our understanding of the various behavioral, endocrine, immune, and neurochemical responses that are correlates of major depression, and that may be reversed or altered by antidepressants. However, despite the variety of models available, none, with the possible exception of the social interaction model, pioneered by Mitchell and Redfern (39), have been refined to detect onset of action. As much attention and resources are now being directed toward the need to find faster acting antidepressants (41), complimentary animal models are needed.

The olfactory bulbectomized rat has been validated as a model of depression over the past 20 years (29). It has the advantage over many other models in that many of its behavioral changes occur following chronic but not acute antidepressant treatment, which correlates well with the typical delayed onset of action seen in the clinical setting (29). In addition, it exhibits many neurochemical, endocrine, and immunological changes that correspond with those seen in clinical depression (27,28,49).

In the present study we assessed the ability of the bulbectomized rat to detect an earlier onset of antidepressant action of the SSRI paroxetine in combination with the full 5-HT_{1A} antagonist WAY-100635 (N-{2[4-(2-methoxyphenyl)-1-piperazinyl]ethyl}-N-(2-pyridines)cyclo-hexane carboxamide trihydrochloride). The attenuation of the bulbectomy-induced hyperactivity in the open field by antidepressants following chronic (usually 14 days) treatment has been one of the most consistently reproducible paradigms of the olfactory bulbectomy syndrome (51). In the present study we have investigated the effects of 3, 7, and 14 days, combined WAY 100635 and paroxetine treatment on this response. As we have previously demonstrated that the nonselective 5-HT_{1A} receptor antagonist, pindolol, counterintuitivly antagonizes the effects of paroxetine in the OB rat following 14 days of administration (12), it is, therefore, of interest to assess the effects of a selective 5-HT_{1A} antagonist on this response.

In addition to changes in locomotor activity following paroxetine and WAY 100635 alone and in combination, we also assessed the effects of these treatments on 5-HT_{1A} receptor function, by challenging each rat with the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and measuring the degree of hypothermia obtained. The attenuation of 8-OH-DPAT–induced hypothermia has been shown to occur following chronic antidepressant treatment and also by electroconvulsive shock therapy (20,21). This paradigm is introduced to complement the behavioral data and to give an insight into the functional activity of the 5-HT_{1A} receptor over the treatment period.

METHOD

Animals

Male Sprague–Dawley rats (SPF, Perth, Australia) (300–350 g) were brought into the laboratories and allowed to acclimatize for 1 week prior to any intervention. The animals were housed four per cage in standard hard-bottom polypropylene cages (45 × 28 × 20 cm), containing wood shavings and with stainless steel lids. The animals had ad lib access to food and water. The animals were maintained at a constant temperature (room temperature of 21 ± 1°C) and at standard lighting conditions (12 h light; 12 h dark, lights on from 0800 to 2000 h). They were handled daily prior to surgery. All procedures were carried out under the guidelines of the animal welfare committee of the Austin and Repatriation Medical Centre, Heidelberg, Victoria, Australia.

Olfactory Bulbectomy

Bilateral olfactory bulbectomy was performed on rats anesthetized with a 2.5% w/v 2-2-2 tribromo–ethanol anesthesia (Aldrich, Sydney) (10 ml/kg), essentially as described by Cairncross et al. (9). The head was shaved and a midline sagittal incision was made extending at least 1 cm rostral to bregma. Pressure was applied to ensure that the periostium on the underlying bone had been penetrated. A burr hole was drilled at points 7 mm anterior to bregma and 2 mm either side of the midline at a point corresponding to the posterior margin of the orbit of the eye. The olfactory bulbs were removed by suction, and the burr holes filled with a hemostatic sponge (Spongestan, Johnson and Johnson, Sydney). Tetracycline powder was applied to the wound prior to closure using surgical clips. Sham-operated animals received the same treatment; although the dura above the bulbs was punctured, the bulbs were left intact. The animals were given 14 days to recover following surgery prior to drug administration, and were handled daily to eliminate any aggressiveness that may otherwise arise (32).

Drug Treatment

Olfactory bulbectomized and sham-operated animals were each assigned to four treatment groups (n = 6–9) to which paroxetine (5 mg/kg IP), (SmithKline Beecham, Harlow, UK) dissolved in dimethyl sulphoxide (Sigma, Sydney) or vehicle (dimethyl sulphoxide) were administered intraperitoneally in the morning for 14 days. Animals were pretreated with either WAY 100635 (0.2 mg/kg b.i.d. SC), (Wyeth Australia, Sydney) or vehicle (dimethyl sulphoxide). All drugs were administered in an injection volume of 1 ml/kg. Doses were selected based on previous studies using these compounds (12,17,43).

Open Field

The open-field test was conducted on bulbectomized rats and their sham-operated controls on the morning following 3, 7, and 14 days of of drug administration, i.e., 24 h following the last injection. Each rat was placed singly into the center of the open-field apparatus (22). This apparatus consisted of a circular base, 90 cm in diameter, which was divided into three circular sectors. The first consists of a circle in the middle of apparatus 10 cm in diameter; the next consists of a circle subdivided into eight segments from the inner circle out. This has a diameter of 50 cm, and the final sector consists of the space between the middle circle and the outer wall and is subdivided into 16 equivalent sectors. All areas are marked by faint black lines. The wall surrounding the base is bright in color (75 cm in height). Illumination was provided by a 60-W bulb, positioned 90 cm above the floor of the apparatus. All measurements were carried out in a darkened room. The number of segments crossed by each rat over a 3-min period was recorded.

Effect of 8-OH-DPAT on Rectal Temperature

The effect of 8-OH-DPAT (RBI Natick, MA) on rectal temperature of each rat was determined on days 3, 7, and 14 of the study, 6 h following that day's treatment. Each rat was challenged with an injection of 8-OH-DPAT (0.15 mg/kg, SC). Core body temperatures were taken by inserting a digital rectal thermometer 3 cm into the rectum. The rats were lightly restrained during the procedure. A steady readout of its temperature was obtained usually after approx. 30 s following insertion of the probe.

Statistical Analysis

Initially, a three-way repeated measures (time/lesion/drug treatment) analysis of variance (ANOVA) was performed on the data. To verify any potential interaction effects between the combination and the drug alone groups, a second three-way repeated measures (time/combination/drug alone), ANOVA was performed on the data. If any statistically significant changes were found, the data was further analyzed using post hoc Student–Newman–Keuls tests. All results were considered significant at $p < 0.05$.

RESULTS

Open-Field Test

ANOVA revealed a significant effect of time, $F(2, 135) = 13.12$, $p < 0.0001$); of lesion, $F(1, 135) = 154.09$, $p < 0.0001$, and of drug treatment, $F(3, 135) = 4.11$, $p < 0.008$, on the ambulation scores of rats placed in the open-field apparatus. There was a significant increase in open-field ambulation in the olfactory bulbectomized control group when compared to its corresponding sham-operated animal following 3, 7, and 14 days of treatment. Post hoc analysis revealed that paroxetine alone and in combination with WAY 100635 significantly attenuated this increase following 14 days of treatment only, whereas all other treatment regimes at all time points failed to alter this hyperactivity (see Fig. 1).

8-OH-DPAT Challenge

There was a substantial drop in temperature recorded in control animals 30 min following the 8-OH-DPAT challenge. ANOVA revealed a significant effect of time, $F(2, 135) = 79.28$, $p < 0.0001$, and of drug treatment, $F(3, 135) = 48.02$, $p < 0.0001$, on the alterations in core body temperature in rats challenged with 8-OH-DPAT, while there was no significant effect of lesion on the response. However, the second ANOVA failed to show any statistically significant interaction effect between paroxetine alone or in combination with WAY 100635. Following 3 days treatment post hoc analysis revealed a significant attenuation in the olfactory bulbectomized com-

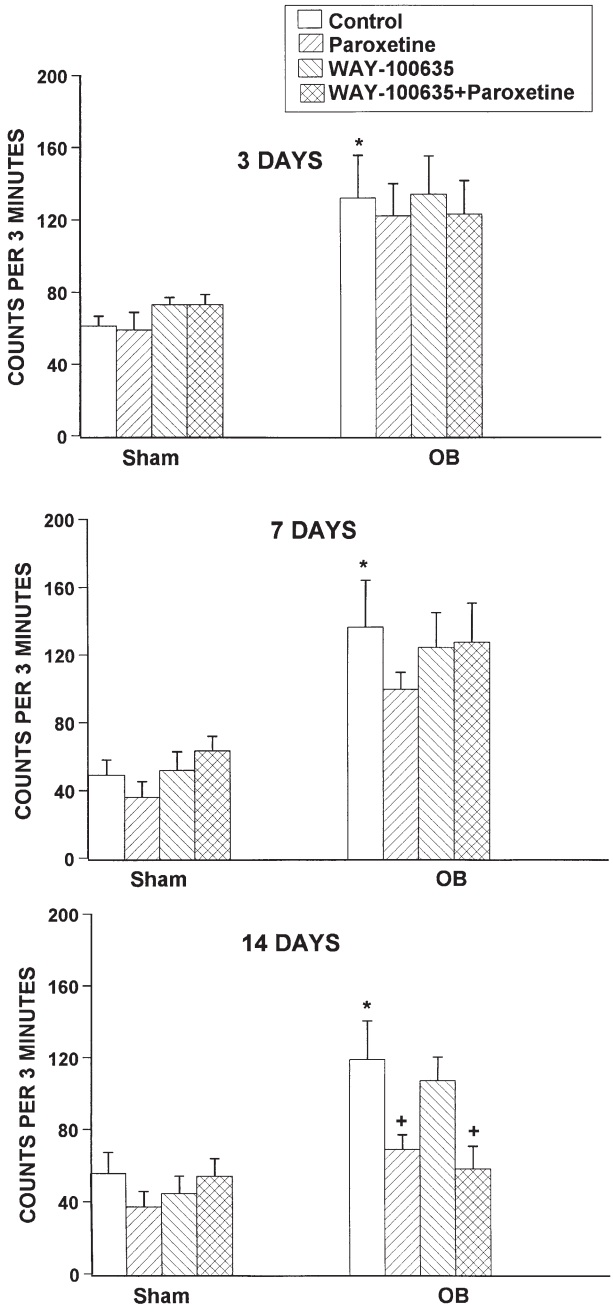

FIG. 1. The effects of 3, 7, or 14 days of treatment with WAY 100635 and paroxetine alone and in combination, on olfactory bulbectomy-induced hyperactivity in the open field. Data represents means with standard errors of six to nine animals. $^{*}p < 0.05$ vs. sham control; $^{+}p < 0.05$ vs. olfactory bulbectomized control (Student–Newman–Keuls tests).

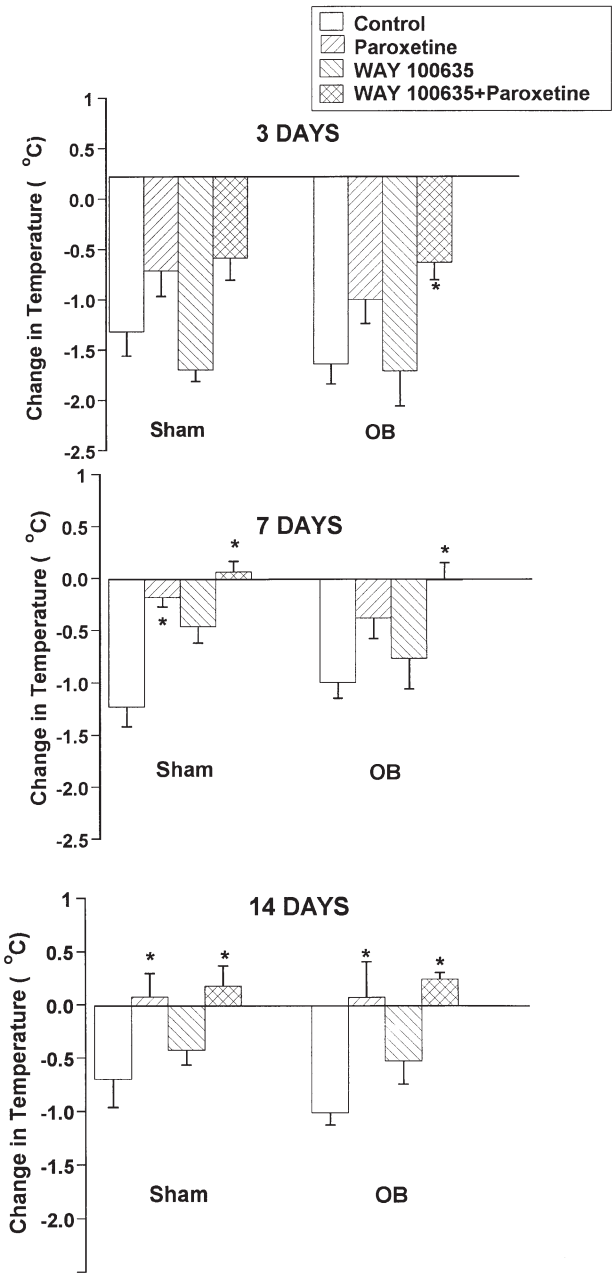

FIG. 2. The effects of 3, 7, or 14 days of treatment with WAY 100635 and paroxetine alone and in combination, treatment on 8-OH-DPAT–induced hypothermia in the olfactory bulbectomized rat. Data represents means with standard errors of six to nine animals. $^*p < 0.05$ vs. relevant control (Student–Newman–Keuls tests).

bination group, with a trend towards significance in the corresponding sham group. Neither of the other two groups had a significantly altered hypothermic response to 8-OH-DPAT. Following 7 days of treatment post hoc analysis revealed a complete reversal of the hypothermic response in both the olfactory bulbectomized and sham-operated combination groups. This attenuation was much more robust than that seen after 3 days of treatment. There was also a signifciant attenuation of the DPAT-induced hypothermic effects in the sham-operated paroxetine group, with a trend towards significance seen in the corresponding OB group. Subsequent to 14 days of treatment, Newman–Keuls post hoc analysis revealed that the hypothermic response was reversed in both the olfactory bulbectomized and sham-operated paroxetine and combination groups. WAY 10035 alone failed to have any effect on 8-OH-DPAT–induced hypothermia in either olfactory bulbectomized or sham-operated animals (see Fig. 2).

DISCUSSION

This study confirms that conventional antidepressants, like paroxetine, are only active following chronic treatment in the olfactory bulbectomized rat model of depression. The addition of a full 5-HT_{1A} receptor antagonist to the SSRI is unable to accelerate the onset of its behavioral effects. This attenuation of the olfactory bulbectomy-induced hyperactivity by paroxetine after 14 day treatment is consistent with previous studies (12,36,43). It suggests that this behavioral facet of the olfactory bulbectomy model is not sensitive to the detection of an earlier onset of antidepressant action due to combinations of 5-HT_{1A} receptor antagonists and SSRIs. Our previous studies with combinations of paroxetine and pindolol also suggested this (12). However, in contrast to these studies, where pindolol actually antagonized the effects of paroxetine in the open field following 14 days of treatment, WAY 100635 did not affect paroxetine's attenuation of OB-induced hyperactivity. This suggests that a factor independent of pindolol's effect at 5-HT_{1A} receptors may be responsible for such antagonism. The olfactory bulbectomized rat model is sensitive to the actions of most clinically effective antidepressants after chronic administration only [see (29)]. However, the exact biochemical basis of the effects of antidepressants in this model are far from understood. Clearly, additional work is necessary to elucidate the neurochemical basis of the antagonist effect of pindolol on paroxetine in this model and the lack of effect of WAY 100635. Whether this effect is relevant to the mechanism of action of antidepressants in the model awaits further research.

There appears to be little effect of repeated exposure to the open-field apparatus in either sham or OB animals, at least for the short time employed in this experiment. This is the first time this has been demonstrated in OB animals. In previous studies using the model, separate groups of animals have always been used for each time point (12,37,44). This present study clearly shows that the need for this is circumvented as far as behavioral end points are concerned.

In addition, an alteration to the 5-HT_{1A} receptors following combined WAY 100635 and paroxetine treatment in both sham and olfactory bulbectomized-operated animals has been demonstrated. This adaptational change, as manifested by the attenuation of 8-OH-DPAT–induced hypothermia, appears to be slightly faster with the combined treatment than with paroxetine alone. This is consistent with our previous studies with pindolol (12). Nonetheless, as no statistically significant interaction effect between the drug alone or in combination with WAY 100635 was observed, this effect cannot be overstated. Whether this hypothermic response to 8-OH-DPAT is a pre- or postsynaptic 5-HT_{1A} receptor-mediated effect remains uncertain [see (13)], and thus complicates the interpretation of the present findings. Chronic paroxetine treatment has previously been suggested to cause a desensitization of both pre- and postsynaptic 5-HT_{1A} receptors (46). It is generally assumed that pindolol may exert its effects both in the clinic and in preclinical studies by selectively blocking presynaptic (somatodendritic) 5-HT_{1A} receptors (4,38), while the

concurrent reuptake blockade by paroxetine causes an increase in synaptic 5-HT. It can, therefore, be hypothesized that the subsequent enhanced inter synaptic concentrations of 5-HT may lead to a rapid postsynaptic 5-HT_{1A} receptor desensitization/downregulation that may manifest as a blunting of the hypothermic response to 8-OH-DPAT, as we have previously shown (12). WAY 100635, however, is a full antagonist at both pre- and postsynaptic 5-HT_{1A} receptors (17), and yet exerts a similar profile of blunted 8-OH-DPAT–induced hypothermia (i.e., faster desensitization of the 5-HT_{1A} receptor) as that seen with pindolol, when combined with paroxetine. It can be suggested, therefore, that blockade of the presynaptic receptor is probably the key to the faster attenuation of 8-OH-DPAT–induced hypothermia by antagonist/antidepressant combinations. It is noteworthy that repeated treatment with WAY 100635 itself causes no significant alteration in the degree of hypothermia. There appears to be a slight blunting of the response following chronic treatment; nonetheless, this must be seen in context of a slight attenuation of the hypothermic effect following repeated challenge in the control groups also.

While the mechanism of action of the WAY 100635–paroxetine combination on 8-OH-DPAT–induced hypothermia may be disputed, we have shown once again that this paradigm is sensitive to potential faster acting antidepressant combinations, albeit not as potently as the combinations with pindolol, and is able to detect 5-HT_{1A} receptor-mediated effects as early as 3 days after commencing treatment. Again, as previously suggested, the changes in 5-HT_{1A} receptor sensitivity do not seem to be related to the direct action of paroxetine on the 5-HT transporter in the olfactory bulbectomy model. This is consistent with the lack of a lesion effect on the hypothermic response in the olfactory bulbectomized rat in this and previous studies (10–12). Despite this, one can only envisage the attenuation of 8-OH-DPAT–induced hypothermia as a model of 5-HT_{1A} receptor function rather than one of antidepressant action. Accordingly, there have been inconsistent effects seen with some antidepressants [(33,36,52) and Cryan et al., unpublished observations]. Nevertheless, it gives an invaluable insight into the functioning of one of the key receptor subtypes involved in the antidepressant response.

The bulbectomy model has failed to detect any potential faster action of WAY 100635 or pindolol in combination with paroxetine. It also has been recently tested to see whether any potential faster onset may be seen with the serotonin–noradrenaline reuptake inhibitor venlafaxine (44) as well as the combination of the selective noradrenaline reuptake inhibitor, reboxetine with the SSRI sertraline (37), with no diminution of the time of onset seen. Despite this, it may be premature to rule out the olfactory bulbectomy model completely as a method of detecting faster acting antidepressants due to the lack of any positive control. The clinical findings with pindolol, although suggesting a faster acting antidepressant response, can still be regarded as tentative, and requires unequivocal confirmation in more large-scale placebo-controlled trials (6,50).

ACKNOWLEDGEMENTS

The authors would like to thank SmithKline Beecham (Harlow, UK) and Wyeth-Australia (Sydney) for the generous gift of paroxetine and WAY 100635, respectively.

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