Full Agonistic Properties of Bay x 3702 on Presynaptic and Postsynaptic 5-HT$_{1A}$ Receptors Electrophysiological Studies in the Rat Hippocampus and Dorsal Raphe.

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ABSTRACT
The present studies evaluated the effects of acute and long-term administration of the 5-HT$_{1A}$ agonist BAY x 3702 on the responsiveness of dorsal raphe 5-HT neurons and of dorsal hippocampus CA$_3$ pyramidal neurons. BAY x 3702 potently reduced the firing activity of 5-HT neurons and of CA$_3$ pyramidal neurons when applied by microiontophoresis and this inhibitory effect of BAY x 3702 was fully antagonized by low intravenous doses of the 5-HT$_{1A}$ antagonist WAY 106835. Concurrent microiontophoretic application of BAY x 3702 did not antagonize the suppressant effect of firing activity on postsynaptic firing activity of 5-HT and CA$_3$ pyramidal neurons. Sustained administration of BAY x 3702 for 2 days (1 and 1.25 mg/kg/day using osmotic minipumps implanted subcutaneously) markedly decreased the firing rate of dorsal raphe 5-HT neurons. This was followed by a full recovery to normal after only 7 days of treatment. The postsynaptic 5-HT$_{1A}$ receptors in the hippocampus, contrary to the presynaptic 5-HT$_{1A}$ receptors, were not desensitized after a 14-day treatment. In conclusion, BAY x 3702 acted as a full and potent agonist both at somatodendritic 5-HT$_{1A}$ autoreceptors and at postsynaptic 5-HT$_{1A}$ receptors. Long-term administration of BAY x 3702 resulted in a desensitization of the somatodendritic 5-HT$_{1A}$ autoreceptors, but in an unaltered responsiveness of 5-HT$_{1A}$ receptors on pyramidal neurons. These results suggest that sustained administration of BAY x 3702 enhances neurotransmission at postsynaptic 5-HT$_{1A}$ receptors.

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addition, biochemical results suggest that BAY x 3702 may be a full 5-HT₁₅ receptor agonist (De Vry et al., 1998).

The present in vivo electrophysiological experiments were performed to evaluate the effects of acute and those of long-term administration of BAY x 3702 on the responsiveness of somatodendritic 5-HT₁₅ autoreceptors of dorsal raphe 5-HT neurons and on postsynaptic 5-HT₁₅ receptors of dorsal hippocampus pyramidal neurons. The latter experiments were deemed of great interest because the effects of a full 5-HT₁₅ agonist on the sensitivity of postsynaptic 5-HT₁₅ receptors had not yet been examined because such drugs were not available.

Materials and Methods

Animals. Electrophysiological experiments were performed in male Sprague-Dawley rats (250–300 g) anaesthetized with chloral hydrate (400 mg/kg, i.p.) and supplemental doses being given throughout the experiment to maintain constant anaesthesia. Animals were kept in standard laboratory conditions (12:12 light/dark cycle with free access to food and water, at a room temperature of 21 ± 2°C). They were placed in a stereotaxic apparatus and their body temperature was maintained at 37°C throughout the experiments.

Treatment. The rats (weight: 150–200 g) were anaesthetized with fluothane in a vehicle containing a 2:1 O₂/N₂O mixture, and osmotic Alzet 2 ML2 minipumps (Alza, Palo Alto, CA, USA) with BAY x 3702 at a delivery rate of 0.5, 1.0 or 1.25 mg/kg/day were implanted subcutaneously. Control rats were implanted with osmotic minipumps containing physiological saline. All electrophysiological experiments were carried out with the minipump in place in order to mimic the clinical condition: patients undergo an improvement of their depressive condition while taking medication and not upon withdrawal. In fact, patients often rapidly relapse if their medication is stopped immediately after achieving remission. Treatment periods were of 2, 7 and 14 days.

Preparation of electrophysiological experiment. The extra-
cellular recordings were carried out using single- or five-barrelled glass micropipettes (R & D Scientific Glass, Spencerville, MD). The single micropipettes were used for recording dorsal raphe 5-HT neurons and their tips were of 1–3 μm in diameter. The five-barrelled micropipettes were used to record C₅ dorsal hippocampus pyramidal and dorsal raphe 5-HT neuron, with their tips broken back to 8–12 and 5–7 μm in diameter. The five-barrelled micropipettes were used before and after each intravenous injection (through a lateral tail vein) of the selective 5-HT₁₅ antagonist WAY 100635 (Fletcher et al., 1996). The pyramidal neurons were identified by their large amplitude (0.5–1.2 mV) and long-duration (0.8–1.2 msec) simple action potentials, alternating with complex spike discharges (Kandel and Spencer, 1961). Because most hippocampus pyramidal neurons are not spontaneously active under chloral hydrate anaesthesia, a small ejection current of ACh (0–5 nA) was used to activate them within their physiological firing rate (8–15 Hz; Ranck, 1975). This exogenous activation of these neurons does not interfere with the detection of altered neuronal responsiveness produced by antidepressant treatments since alterations can be put into evidence using both this approach and a low cerebroisolate without anaesthesia (de Montigny and Aghajanian, 1978; de Montigny, 1984; de Montigny et al., 1984). The responsiveness of neurons to microiontophoretic application of the drugs was expressed as the number of spikes suppressed. The value was calculated by an on-line computer. Microiontophoretic ejection periods (5-HT, BAY x 3702 and GABA) were kept constant at 50 sec, and 8-OH-DPAT ejection periods were kept constant at 40 sec. The number of spikes suppressed by the ejections of 8-OH-DPAT and BAY x 3702 was calculated as the spikes missing below baseline in a 90-second interval from the beginning of the microiontophoretic application (Chaput et al., 1986).

Drugs. 5-HT creatinine sulphate, ACh and quisquulate were purchased from Sigma Chemicals (St. Louis, MO, USA); 8-OH-DPAT from RBI (Natick, MA, USA); and GABA from Calbiochem (Los Angeles, CA). BAY x 3702 ((-)-R)-2-[4-[(3,4-dihydro-2H-1-benzazepin-2-yl)methyl]-amino]butyl-11,12-benzothiazol-3(2H)-one 1,1-dioxide monohydrochloride or (−)-(R)-2-[4-[(3-chroman-2-ylmethyl)-amino]butyl]-1,1-dioxo-1,2-benzothiazol-3(2H)-one monohydrochloride was provided by Troponwerke (Wuppertal, Germany), and WAY 100635 by Wyeth Research (Princeton, NJ).

Statistical analysis. All results are expressed as mean ± S.E.M. In all the cases, the n refers to the number of neurons tested. Pearson’s r and ED₅₀ values for the dose-response curves were calculated by simple linear regression analysis. The degree of statistical significance of the difference between ED₅₀ values of saline-treated and BAY x 3702-treated rats was calculated with 95% confidence limit method. T₅₀ value analysis was also used in our microiontophoretic experiments (I being the current in nA, and T₅₀ the time required to suppress the firing activity by 50%). This value is expressed as nanocoulombs (nC; de Montigny et al., 1980; de Montigny and Aghajanian, 1977). Both values were calculated by an on-line computer. Microiontophoretic ejection periods were kept constant at 50 sec, and 8-OH-DPAT ejection periods were kept constant at 40 sec. Statistical comparisons between control and treatment groups were carried out by using the two-tailed Student’s t-test.
Results

Effect of acute BAY x 3702 administration on the firing frequency of 5-HT neurons in the dorsal raphe.
In order to assess the effectiveness of BAY x 3702 in reducing the firing activity of 5-HT neurons, a single dose was administered intravenously to 12 rats. As illustrated in figure 1A, small doses of BAY x 3702 dose-dependently reduced the spontaneous firing activity of 5-HT neurons recorded in the dorsal raphe at the dose range of 0.1–1.0 μg/kg (fig. 1B). The ED_{50} of this suppressant effect of intravenous BAY x 3702 on the firing activity of 5-HT neurons was of 0.45 ± 0.05 μg/kg. The firing activity of dorsal raphe 5-HT neurons was also reduced by microiontophoretic applications of BAY x 3702 and 5-HT (fig. 2). BAY x 3702 produced a much greater suppressant effect of firing activity than ipsapirone when applied by microiontophoresis onto the same neuron using the same concentration (ipsapirone: 26 ± 6, BAY x 3702: 125 ± 29 spikes suppressed, P < 0.01, n = 8). Consistently with the results obtained with systemic administration, BAY x 3702 was very potent in suppressing firing activity of 5-HT neurons, as evidenced by the 1 nA current producing a mean inhibitory effect of 70% in 11 neurons (see fig. 2). Using the IT_{50} method to assess the potency of BAY x 3702, a value of 24 ± 4 nA (n = 11) was obtained. The suppressant effect of the intravenous BAY x 3702 was blocked by WAY 100635 (0.25 mg/kg, i.v.; n = 6). Concurrent application of BAY x 3702 did not produce any alteration of the effectiveness of 5-HT in inhibiting pyramidal neurons firing activity (5-HT alone: 7.9 ± 1.1, 5-HT with BAY x 3702: 7.3 ± 1.1 spikes suppressed, P > 0.05, n = 11), applied through the same microinjection pipette (fig. 2). Quisqualate was used to maintain the firing activity of 5-HT neurons when concurrent application of BAY x 3702 was carried out.

Effect of acute BAY x 3702 administration on the firing activity of CA_3 pyramidal neurons in the dorsal hippocampus. Partial 5-HT_{1A} agonists, applied microiontophoretically, reduce the firing activity of dorsal hippocampus pyramidal neurons by increasing membranal hyperpolarization (Sprouse and Aghajanian, 1986; Blier and de Montigny, 1990; Godbout et al., 1991). In order to compare the potency of BAY x 3702 with that of ipsapirone, they were applied by microiontophoresis onto the same neurons using the same concentration. BAY x 3702 produced a much greater suppressant effect of firing activity than ipsapirone (fig. 3; ipsapirone: 92 ± 17, BAY x 3702: 2889 ± 450 spikes suppressed, P < 0.01, n = 10). Using the IT_{50} method to assess the potency of BAY x 3702, a value of 41 ± 3 nC (n = 17) was obtained. The intravenous administration of the 5-HT_{1A} antagonist WAY 100635 at a dose of 0.25 mg/kg completely blocked the suppressant effect of BAY x 3702, and restored above the baseline firing activity after application of BAY x 3702 which had produced a prolonged suppression of firing (n = 4; fig. 4). However, the concurrent application of BAY x 3702 did not produce any reduction of the effectiveness of 5-HT in inhibiting pyramidal neurons firing activity (5-HT alone: 764 ± 38, 5-HT with BAY x 3702: 732 ± 37 spikes suppressed, P > 0.05, n = 10), even with ejection currents producing a marked reduction of firing activity that required restoration of baseline firing activity through a high ACh current (fig. 4).

Effect of sustained BAY x 3702 administration on the firing activity of dorsal raphe 5-HT neurons. At a dose of 0.5 mg/kg/day, sustained administration of BAY x 3702 delivered for 2 days by minipumps altered neither the mean number of active 5-HT neurons per descent nor their rate of firing (Table 1). At a regimen of 1.0 mg/kg/day, the number of
spontaneously active neurons per trajectory was not different from that obtained in the controls, but their mean firing rate was significantly lower (Table 1). However, using a daily dose of 1.25 mg/kg of BAY x 3702, both the number of spontaneously active 5-HT neurons per descent and their mean firing rate were markedly decreased (fig. 5; table 1). The number of 5-HT neurons recorded per descent was back to normal in 7-day treated rats with the highest dose, as well as their firing rate (fig. 5C; table 1). After a 14-day treatment with 1.25 mg/kg/day, both the firing activity and the number of 5-HT neurons per descent remained within the normal range (fig. 5D; table 1).

Effect of long-term BAY x 3702 treatment on the responsiveness of dorsal raphe 5-HT neurons to microiontophoretic applications of 5-HT, 8-OH-DPAT and GABA. Direct microiontophoretic application of 5-HT, 8-OH-DPAT and GABA was carried out in order to determine whether the responsiveness of somatodendritic 5-HT1A autoreceptors was attenuated following the 14-day BAY x 3702 treatment (fig. 6). The responsiveness of dorsal raphe 5-HT
Effect of intravenous administration of 8-OH-DPAT on the firing activity of 5-HT neurons in control and BAY x 3702-treated rats. Long-term treatment with 5-HT_{1A} agonists desensitizes somatodendritic 5-HT_{1A} autoreceptors without altering the effect of the systemic administration of 8-OH-DPAT on 5-HT neuron firing activity (Blier and de Montigny, 1987; Schechter et al., 1990; Dong et al., 1997). It has thus been proposed that low intravenous doses of 8-OH-DPAT do not exert their suppressant effect on 5-HT neuron firing activity through a direct activation of somatodendritic 5-HT_{1A} autoreceptor, but rather by activating postsynaptic 5-HT_{1A} receptor involved in a negative feedback loop controlling 5-HT neuron firing activity (Blier and de Montigny, 1987; Ceci et al., 1994). In order to determine if the responsiveness of these postsynaptic 5-HT_{1A} receptors activated by low intravenous doses of a 5-HT_{1A} agonist was modified differentially by 14 days of BAY x 3702 administration, dose-response curves for 8-OH-DPAT were constructed in 11 treated rats and 7 controls (fig. 8C). The ED_{50} value in BAY x 3702 treated rats (8.3 ± 1.1 ng/kg i.v.) was significantly different from that obtained in rats treated with saline for 14 days (2.3 ± 0.3 ng/kg, i.v.). The intravenous injection of 0.25 mg/kg WAY 100635 readily reversed the suppressant effect of the 5-HT agonists LSD and 8-OH-DPAT on the firing rate of 5-HT neurons in 5 controls and 5 treated rats (fig. 8, A and B).

Effect of long-term BAY x 3702 treatment on the firing activity of CA_{3} dorsal hippocampus pyramidal neurons. BAY x 3702 did not alter the effectiveness of microiontophoretically-applied 5-HT and 8-OH-DPAT in suppressing the firing activity of pyramidal neurons of the CA_{3} dorsal hippocampus in the rats treated for 14 days using sustained administration (fig. 9). The average microiontophoretic ejection currents of ACh used to activate CA_{3} pyramidal neurons were not different in control group (1.13 ± 0.1 nA, n = 22) and group of treated rats (1.12 ± 0.1 nA, n = 22). In order to assess the degree of tonic activation of postsynaptic 5-HT_{1A} receptors, the highly selective 5-HT_{1A} antagonist WAY 100635 was injected intravenously in control and BAY x 3702 14-day treated rats. Should a treatment produce an enhanced activation of these receptors, a disinhibition should result from their antagonism given that they exert an inhibiting effect on pyramidal neuron firing activity. As previously observed (Haddjeri et al., 1997; Rueter et al., 1998), WAY 100635 (0.25 mg/kg, i.v.) did not enhance firing activity in four control rats. Similarly, it also did not enhance pyramidal neuron firing activity after the 14-day BAY x 3702 treatment in 5 rats, despite attenuating significantly the effectiveness of microiontophoretic administration of 5-HT (fig. 10).

Discussion

The present in vivo electrophysiological studies show that BAY x 3702 potently reduced the firing activity of 5-HT neurons in the dorsal raphe and of CA_{3} pyramidal neurons in the dorsal hippocampus by activating 5-HT_{1A} receptors because its inhibiting effect was reversed and prevented by the selective 5-HT_{1A} antagonist WAY 100635. BAY x 3702 acted as a full agonist at both pre- and postsynaptic 5-HT_{1A} receptors. Its long-term administration resulted in a desensitization of somatodendritic 5-HT_{1A} autoreceptors (resulting in
the normalization of firing activity of 5-HT neurons), but in an unaltered responsiveness of 5-HT\textsubscript{1A} receptors on pyramidal neurons.

The firing activity of the dorsal raphe 5-HT neurons can be reduced by acute intravenous administration of 5-HT\textsubscript{1A} agonists (Blier and de Montigny, 1987; Sprouse and Aghajanian, 1987). BAY x 3702, like partial 5-HT\textsubscript{1A} agonists (e.g. gepirone, ipsapirone), can inhibit completely 5-HT neuron firing activity recorded extracellularly with very small intravenous doses. The potency of BAY x 3702 was also much greater than that of ipsapirone on both 5-HT and pyramidal neurons. The recovery of firing activity of 5-HT neurons and of pyramidal neurons was also much prolonged after microiontophoretic application of BAY x 3702 (figs. 1–4). This prolonged recovery suggests that the dissociation of BAY x 3702 from the 5-HT\textsubscript{1A} receptors occurs very slowly, as exemplified in figure 4 where the 5-HT\textsubscript{1A} antagonist WAY 106635 readily reversed the residual inhibitory effect of BAY x 3702 (fig. 4). Using the \textit{IT\textsubscript{50}} method to compare the effectiveness of BAY x 3702 to suppress firing activity, it was shown that this agent was more potent in the raphe than in the hippocampus, like other agents with partial 5-HT\textsubscript{1A} agonistic property being more potent in raphe than in the hippocampus (Blier and de Montigny, 1987; Dong et al., 1997). The concurrent microiontophoretic application of BAY x 3702 did not antagonize the suppressant effectiveness of 5-HT on the firing activity of the dorsal raphe 5-HT neurons and of the CA\textsubscript{3} pyramidal neurons (figs. 2 and 4). This indicates that BAY x 3702 is a full 5-HT\textsubscript{1A} receptor agonist at pre- and postsynaptic 5-HT\textsubscript{1A} receptors. In contrast, selective 5-HT\textsubscript{1A} agonists have exhibited different 5-HT activity, resulting from their intrinsic agonistic activity effects in the same paradigm used in the present study (Blier and de Montigny, 1987; de Montigny et al., 1991; Godbout et al., 1991; Hadrava et al., 1995; Dong et al., 1997). The rank order the apparent antagonistic activities of the 5-HT\textsubscript{1A} agonists tested, as assessed by the degree of suppression (\%) of the effect of 5-HT on the firing rate of pyramidal neurons in the CA\textsubscript{3} dorsal hippocampus, is as follows: 8-OH-DPAT (92%) > flesinoxan (85%) \geq gepirone (70%) > tandospirone (57%) > ipsapirone (31%) > BAY x 3702 (0%). In all instances, these data were obtained with an ejection current of the 5-HT\textsubscript{1A} agonist adjusted to produce a 50–80% suppression of the firing activity of dorsal hippocampus CA\textsubscript{3} pyramidal neurons, the latter being restored by increasing the ejection current of quisqualate or of ACh. BAY x 3702 therefore displayed full intrinsic activity at 5-HT\textsubscript{1A} receptors in the dorsal hippocampus.

Sustained administration of BAY x 3702 (1.25 mg/kg/day) for 2 days produced a marked decrease of the firing activity of dorsal raphe 5-HT neurons and of the number of spontaneously active 5-HT neurons per micropipette descent through the dorsal raphe nucleus (fig. 5, table 1). This was followed by a gradual recovery of both parameters which were back to normal after 7 days of treatment, unlike other 5-HT\textsubscript{1A} agonists, MAOIs and SSRIs, which have been shown to significantly attenuate these parameters even after such a treatment period. This difference might be related to the greater potency of this drug.

A previous study showed that the 5-HT\textsubscript{1A} agonist ipsapirone (10 mg/kg, i.p. twice daily) reduces the density of 5-HT\textsubscript{1A} binding sites labelled with \textsuperscript{3}H\textsubscript{8}-OH-DPAT in the dorsal raphe nucleus, but not in the dorsal hippocampus (Fanelli and McMonagle-Strucko, 1992). However, no change in the density of 5-HT\textsubscript{1A} receptor binding sites was detected by Schechter et al., (1990) in any of the brain areas examined after a two-week treatment with a lower dose of ipsapirone (5 mg/kg, i.p., twice a day). The latter investigators also found that somatodendritic 5-HT\textsubscript{1A} autoreceptors were nonetheless desensitized in the dorsal raphe by this low dose of ipsapirone. Hence, taken together, these results indicate that high doses of a 5-HT\textsubscript{1A} agonist can down-regulate the density of somatodendritic 5-HT\textsubscript{1A} autoreceptors in the dorsal raphe. However, a functional desensitization can also occur in the absence of any detectable alteration of the binding parameters of these receptors, as was also the case with the SSRI cericlamine (Jolas et al., 1994). In fact, it has been suggested that SSRIs desensitize 5-HT\textsubscript{1A} autoreceptors by decreasing the amount of Gi/o proteins (Li et al., 1996). It is thus likely...
that 5-HT\textsubscript{1A} agonists also desensitize the 5-HT\textsubscript{1A} autoreceptor by the same mechanism.

BAY x 3702 given in a sustained fashion markedly reduced the response of 5-HT neurons to both the intravenous and microiontophoretic administration of 8-OH-DPAT (figs. 6–8). In contrast, similar treatments with partial 5-HT\textsubscript{1A} agonists modified only the effect of microiontophoretically-applied 8-OH-DPAT on the firing activity of dorsal raphe 5-HT neurons (Blier and de Montigny, 1987). A first possibility to envisage for these different results is the marked potency of BAY x 3702 when compared to other 5-HT\textsubscript{1A} agonists. A second possibility is that BAY x 3702 is a full 5-HT\textsubscript{1A} agonist. Interestingly, Ceci et al., (1994) have shown that the dose-response curve of the suppressant effect of 8-OH-DPAT on the firing rate of dorsal raphe 5-HT neurons was shifted to the right by about 10-fold following an acute fronto-cortical deafferentation. Therefore, it may be proposed that the desensitization 5-HT\textsubscript{1A} receptors may also be occurring in the frontal cortex, consequentially decreasing the negative feed loop controlling firing activity of dorsal raphe 5-HT neurons. Indeed, it was recently observed that long-term SSRIs administration attenuated the responsiveness of orbitofrontal cortex neurons to microiontophoretically-applied 8-OH-DPAT (El Mansari et al., 1997). Since the acute systemic 5-HT\textsubscript{1A} agonist challenge in long-term BAY x 3702 treated rats does not result in a marked decrease of the firing activity of 5-HT neurons in the dorsal raphe, as it does in gepirone or ipsapirone treated rats, BAY x 3702 may thus be expected to produce a greater enhancement of 5-HT transmission, and possibly a greater therapeutic effect, than the two latter drugs.

The postsynaptic 5-HT\textsubscript{1A} receptors in the hippocampus, contrary to the somatodendritic 5-HT\textsubscript{1A} autoreceptors, were not desensitized during sustained administration of BAY x 3702 even though the compound exhibited a full agonistic property in acute experiments (fig. 9). The lack of desensitization of these receptors following long-term treatment was thus identical to results previously obtained with 5-HT\textsubscript{1A} partial agonists.

WAY 100635 blocked the postsynaptic 5-HT\textsubscript{1A} receptor activated by microiontophoretic application of 5-HT and BAY x 3702. However, WAY 100635 did not enhance hippocampal neuronal firing in rats treated with BAY x 3702 for 14 days, unlike previous results obtained in rats treated with gepirone (Haddjeri et al., 1997). A first possibility to account for these divergent results is that, because of the marked potency and presumably the long dissociation constant of BAY x 3702, WAY 100635 was not able to displace BAY x 3702 from the receptor sites. This interpretation might be consistent with the above mentioned data showing that WAY 100635 increases hippocampus firing activity in gepirone but not flesinoxan-treated rats. Flesinoxan is a very potent 5-HT\textsubscript{1A} agonist which, unlike gepirone and ipsapirone, exerts a prolonged inhibitory effect on the firing activity of pyramidal neurons. A second possibility is that BAY x 3702 potently activates 5-HT\textsubscript{1A} receptors located on the dendrites of pyramidal neurons. These receptors, which can be activated by electrical stimulations of the ascending 5-HT pathway, are blocked by the 5-HT\textsubscript{1A} antagonist BMY 7378 but not by WAY 100635. Another line of evidence for the lack of effect of WAY 100635 on certain hippocampus 5-HT\textsubscript{1A}
receptors is that intravenously injected WAY 100635 does not reverse the inhibitory effect of microiontophoretic application of the 5-HT_{1A} agonist BIMT-17 on pyramidal neurons, whereas, the 5-HT_{1A} antagonist BMY 7378 does (Rueter et al., 1997). These data suggest that WAY 100635 does not block the postsynaptic 5-HT_{1A} receptors apposed to 5-HT terminals on the dendrites of pyramidal neurons (intra-synaptic receptors; Oleskevitch and Descarries, 1990), but does block some 5-HT_{1A} receptors on the cell body of the same neurons (extra-synaptic 5-HT_{1A} receptors) where the recording and microiontophoretic applications are done. In contrast, BMY 7378 would antagonize equally well both populations.

In conclusion, the present results indicate that BAY x 3702 acts as a full and potent agonist at somatodendritic 5-HT_{1A} autoreceptors and at postsynaptic 5-HT_{1A} receptors. The desensitization of somatodendritic 5-HT_{1A} autoreceptors may lead to an enhancement of 5-HT neurotransmission in the hippocampus because the ensuing normalized release of 5-HT, together with the presence of BAY x 3702 throughout the brain, would produce a greater degree of activation of these normosensitive postsynaptic 5-HT_{1A} receptors. These properties of BAY x 3702 should endow this compound with anxiolytic and antidepressant properties in humans. Given that this drug also desensitizes the postsynaptic 5-HT_{1A} receptors which exert an inhibitory effect on 5-HT neuronal firing, it might be expected to have more robust clinical effects than its less potent predecessors endowed with only partial 5-HT_{1A} agonistic properties. In addition, it has been proposed that 5-HT_{1A} agonists may prevent to a significant extent cerebral damage following ischemia (Bielenberg and Burkhardt, 1990). BAY x 3702 has been reported to exert a
neuroprotective effect in animal models of cerebral ischemia (De Vry et al., 1997). Therefore, this drug has therapeutic potential in psychiatric and neurological disorders.

References


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