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5-HT_{1A} receptor agonist effects of BMY-14802 on serotonin release in dorsal raphe and hippocampus

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Abstract

BMY-14802 (BMS-181100; α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine butanol monohydrochloride) is a σ receptor antagonist with potential antipsychotic activity. BMY-14802 also binds to 5-HT_{1A} receptors and is able to inhibit the firing of dorsal raphe serotonergic neurons, suggesting that this compound has 5-HT_{1A} receptor agonist properties in vivo. In the present study, we used in vivo microdialysis to study the effects of BMY-14802 on extracellular serotonin (5-hydroxytryptamine), 5-hydroxyindole-3-acetic acid (5-HIAA) and homovanillic acid (HVA) in the dorsal raphe and ventral hippocampus in the awake rat. Systemic injections of 5–20 mg/kg BMY-14802 induced a simultaneous dose-dependent decrease in 5-HT and markedly increased the dopamine metabolite, HVA concentrations in dialysates from dorsal raphe and hippocampus. Extracellular concentrations of the 5-HT metabolite, 5-HIAA decreased only after 20 mg/kg BMY-14802. The 5-HT decreases in dorsal raphe and hippocampus produced by BMY-14802 were completely antagonized by pretreatment with 1.0 mg/kg of the specific 5-HT_{1A} antagonist, WAY-100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride). These data indicate that BMY-14802 decreases dorsal raphe and hippocampal release of 5-HT by interaction with somatodendritic 5-HT_{1A} receptors in the raphe nuclei and suggest that this compound is a potential anxiolytic.

Keywords: BMY-14802; 5-HT (5-hydroxytryptamine, serotonin); 5-HT_{1A} receptor; Dorsal raphe; Hippocampus; Microdialysis

1. Introduction

BMY-14802 (BMS-181100; α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine butanol monohydrochloride) is a putative antipsychotic with high affinity (IC_{50}) for haloperidol-sensitive σ binding sites (75 nM), moderate affinity for 5-HT_{1A} (199 nM) and α_1 (398 nM) receptors and without significant affinity for dopamine receptors (D_1 > 100 000 nM; D_2 = 6400 nM; Taylor and Dekleva, 1988; Bristow et al., 1991). The potential of BMY-14802 as an antipsychotic came from studies showing that BMY-14802 blocked conditioned avoidance response, inhibited apomorphine-induced stereotypy and had a similar profile as clozapine in some behavioral paradigms (Taylor et al., 1991). Therefore, BMY-14802 was identified as an atypical antipsychotic with a low propensity to cause the extrapyramidal side effects and tardive dyskinesia frequently associated with classical antipsychotic treatment.

Most of the effects of BMY-14802 on the dopaminergic system are thought to be mediated via nondopaminergic sites. For instance, enhanced dopamine synthesis, release, turnover and metabolism in striatum, frontal cortex and olfactory tubercle (Matthews et al., 1986; Rao et al., 1990) and reversal of the effects of apomorphine on dopaminergic midbrain neurons (Wachtel and White, 1988) are thought to be mediated via σ receptors. On the other hand, the protection against methamphetamine-induced dopaminergic neurotoxicity by BMY-14802 was suggested to occur via dopamine receptor antagonism (Terleckyj and Sonsalla, 1994). Taken together, the available data indicate that BMY-14802 interacts with several receptor types and possibly produces antipsychotic effects via interaction with the σ receptor.

In vivo electrophysiological and behavioral data strongly suggest that BMY-14802 has serotonergic effects due to an interaction with the 5-HT_{1A} receptor. For instance, BMY-14802 inhibits the firing of serotonergic dorsal raphe neurons (VanderMaelen and Braselton, 1990) and induces behavioral effects in mice and rats consistent with the

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profile of a typical 5-HT_{1A} agonist. In addition, the increase in firing rate of A9 dopamine neurons by BMY-14802 was suggested to be mediated via 5-HT_{1A} receptors (Zhang et al., 1993). Some of the serotonergic behavioral effects induced by BMY-14802 include hypothermia, the 5-HT syndrome, 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin) discriminative stimuli and antagonism of mescaline-induced head twitches (Bristow et al., 1991).

We have extended these observations by investigating the effects of systemic administration of BMY-14802 on extracellular concentrations of 5-HT, 5-HIAA and HVA in the dorsal raphe and ventral hippocampus in the awake rat. To assess the 5-HT_{1A} receptor selectivity of the effects of BMY-14802 on 5-HT release and metabolite concentrations, we pretreated the animals with the silent and specific 5-HT_{1A} antagonist WAY-100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride); Gurling et al., 1994; Fletcher et al., 1994).

2. Materials and methods

2.1. In vivo microdialysis

Male Sprague-Dawley rats (290–320 g) were anesthetized (i.m.) with a mixture of ketamine HCl (80 mg/kg) and xylazine (6 mg/kg) before implantation of the dialysis probes. To allow the simultaneous measurement of 5-HT, 5-HIAA and HVA from the dorsal raphe and ventral hippocampus, each rat was implanted with two I-shaped fused silica microdialysis probes. The microdialysis tubing (acrylonitrile-sodium methallyl sulfonate membrane, Hospal, Uden, The Netherlands) was coated with epoxy glue, except for a 2 mm (dorsal raphe) or 4 mm (hippocampus) dialysis tip. Probes were implanted stereotaxically using coordinates according to Paxinos and Watson (1986) into the dorsal raphe nucleus A-P +0.7 mm, M-L 0.7 mm (towards midline), D-V 6.8 mm (14° angle) and ventral hippocampus A-P +3.8 mm, M-L 5.0 mm, D-V 7.6 mm.

Microdialysis experiments were carried out 24 h after surgery in freely-moving rats by perfusing the dorsal raphe with artificial cerebrospinal fluid (CSF, NaCl 140.3 mM, KCl 2.7 mM, $CaCl_2$ 2.2 mM, pH 6.5) and the hippocampus with artificial CSF containing 10 μM of the 5-HT reuptake blocker fluoxetine. Probes were perfused at 1.0 μl/min using a microinfusion pump (Carnegie Medicine CMA/100, Lafayette, IN). The dialysates from both brain areas were collected directly into 25 μl loops of injection valves and automatically injected (Digital Valve Sequence Programmer, Valco Instruments, Houston) every 25 min onto the column. After stabilization of baseline dialysate concentrations, BMY-14802 (5–20 mg/kg, i.p.) was injected and the dialysates continuously collected for at least 5 h. In antagonism experiments, WAY-100635 (1.0 mg/kg, i.p.) was injected 50 min before BMY-14802 administration. At the end of the experiments, 0.5% methylene blue dye was perfused through the dialysis probes for at least 60 min. Animals were then anesthetized and the brain removed for the verification of the position of the probes.

2.2. Chromatographic conditions

Dialysate concentrations of 5-HT, 5-HIAA and HVA were measured by high performance liquid chromatography (ODS-Hypersil column; 3 μm, 150 × 3.0 mm; Keystone Scientific, Bellefonte, CA, USA), maintained at 30°C with coulometric detection (ESA Model 5200 Coulochem II, Bedford, MA, USA) using a high sensitivity analytical cell (ESA Model 5011). The first electrode was set at +0.02 V and the second at +0.35 V; a guard cell placed before the injector was set at +0.45 V. The mobile phase consisted of 59 mM potassium phosphate (pH 4.8), 2.3 mM 1-heptanesulfonic acid sodium salt, 1 ml/l triethylamine, 17% methanol and 2% acetronitrile and was delivered at a flow rate of 0.5 ml/min by a Waters 610 pump. Retention time, peak area and peak height were measured with a data management software system (Baseline 810, Waters, Milford, MA, USA). Dialysate concentrations of 5-HT, 5-HIAA and HVA were calculated by comparing peak areas with those of known standards.

2.3. Data presentation and statistical analysis

Data are presented as the mean ± S.E.M. of the percentage decrease or increase of baseline levels. Baseline levels were calculated as the mean of the four sequential samples (25 μl each) prior to drug injection. Arrows in the figures indicate drug administration corrected for the time lag between animal injections and sample collection. Results were analysed using repeated-measures of analysis of variance at various times before and after treatment and between treatment groups followed by Dunnett's two-tail test for multiple comparisons. Statistical significance levels were determined at $P < 0.05$.

2.4. Drugs and chemicals

BMY-14802 (BMS-181100, α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine butanol monohydrochloride) and WAY-100635 (*N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-(2-pyridinyl) cyclohexanecarboxamide trihydrochloride) were synthesized at Bristol-Myers Squibb Pharmaceutical Research Institute (Wallingford, CT, USA); fluoxetine HCl (LY 110140) was a gift from Lilly Research (Indianapolis, IN, USA); 5-hydroxytryptamine HCl (5-HT), 5-hydroxyindole-3-acetic acid (5-HIAA), homovanillic acid (HVA) and triethylamine were purchased from Sigma (St. Louis, MO, USA); 1-heptanesulfonic acid sodium salt from Eastman Kodak (Rochester, NY, USA); methanol from Fisher Scientific (Fair Lawn, NJ, USA) and acetonitrile from J.T. Baker (Phillipsburg, NJ, USA). All other chemicals were analytical grade and obtained from Sigma.

3. Results

3.1. Effects of BMY-14802 on dorsal raphe and hippocampal 5-HT, 5-HIAA and HVA concentrations

Average basal dialysate concentrations of 5-HT, 5-HIAA and HVA from the dorsal raphe were (pg/25 μl ± S.E.M., $n = 21$) 1.6 ± 0.2, 3293 ± 300 and 77.9 ± 7.9, respectively. Since basal dialysate concentrations of 5-HT in the ventral hippocampus were close to our detection limits (approximately 0.3 pg/25 μl), the hippocampus was perfused with artificial CSF containing 10 μM fluoxetine. Under these conditions, control dialysate concentrations were (pg/25 μl ± S.E.M., $n = 21$) 9.3 ± 1.4 for 5-HT, 1165 ± 118 for 5-HIAA and 70.3 ± 15.3 for HVA.

Systemic administration of 5 mg/kg BMY-14802 did not significantly change extracellular 5-HT concentrations in the rat dorsal raphe or ventral hippocampus (Fig. 1). However, 10 and 20 mg/kg BMY-14802 markedly decreased dorsal raphe and hippocampal 5-HT ($P < 0.01$, Fig. 1). In the dorsal raphe, maximal 5-HT decreases to 30% of basal were reached at 75 min after administration of 10 mg/kg BMY-14802 ($P < 0.01$). In the hippocampus, maximal 5-HT decreases to 35% of basal were observed at 75 min after 20 mg/kg BMY-14802 ($P < 0.01$). The effects on 5-HT were reversible: dorsal raphe and hippocampal 5-HT concentrations returned to basal levels within 4 h after injection of 20 mg/kg BMY-14802.

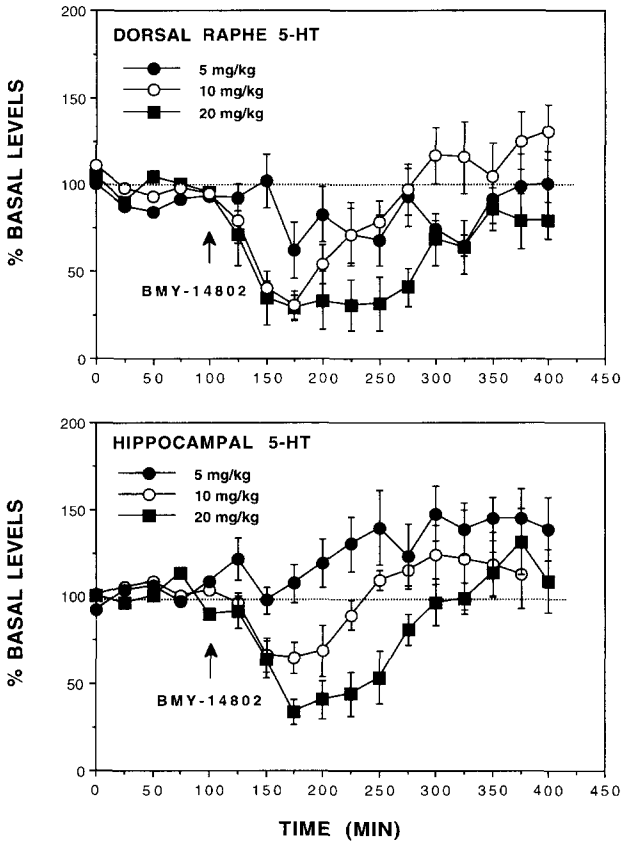

Fig. 1. Time-courses of the effects of BMY-14802 (5–20 mg/kg, i.p., injection at the arrow) on extracellular concentrations of 5-HT in dialysates from dorsal raphe (top) and ventral hippocampus (bottom). Each point represents the mean ± S.E.M. ($n = 5$). Significant decreases in dorsal raphe 5-HT were observed at 125–250 min after 10 mg/kg and at 125–325 min after 20 mg/kg BMY-14802 ($P < 0.01$). Significant decreases in hippocampal 5-HT were observed at 150–200 min after 10 mg/kg and at 150–250 min after 20 mg/kg BMY-14802 ($P < 0.01$).

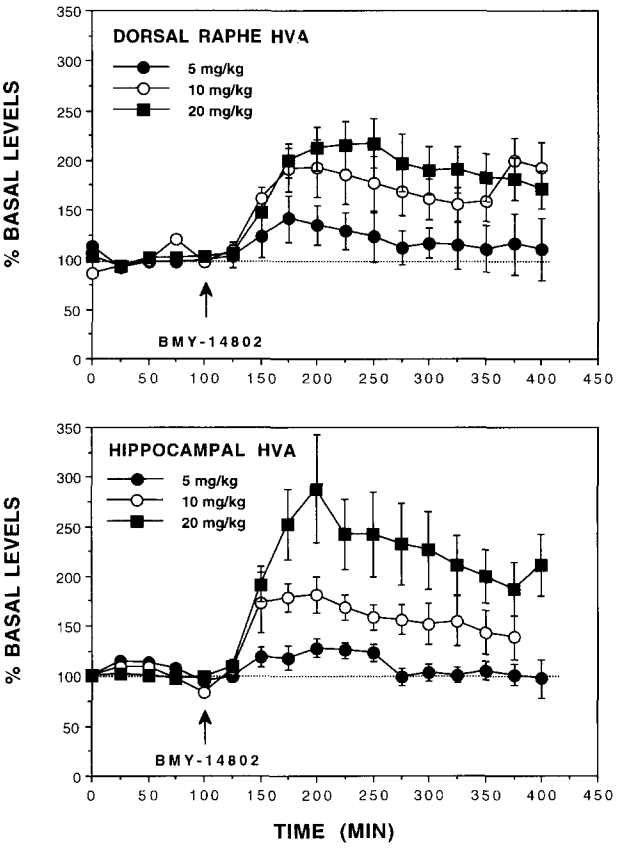

Fig. 2. Time-courses of the effects of BMY-14802 (5–20 mg/kg, i.p., injection at the arrow) on extracellular concentrations of HVA in dialysates from dorsal raphe (top) and ventral hippocampus (bottom). Each point represents the mean ± S.E.M. ($n = 5$). Significant increases in HVA were observed at 175–200 min in the dorsal raphe and at 200–250 min in the hippocampus after 5 mg/kg BMY-14802 ($P < 0.05$). Significant increases in dorsal raphe and hippocampal HVA were observed at 150–400 min after 10 mg/kg and 20 mg/kg BMY-14802 ($P < 0.01$).

In both brain areas, systemic administration of BMY-14802 produced a dose-related and sustained increase in extracellular concentrations of the dopamine metabolite, HVA ($P < 0.01$, Fig. 2). In the dorsal raphe, BMY-14802 induced maximal increases in HVA to 140% after 5 mg/kg ($P < 0.05$), to 190% after 10 mg/kg and to 215% of basal after 20 mg/kg at 75–100 min after injections ($P < 0.01$). In the hippocampus, BMY-14802 increased HVA to 130% after 5 mg/kg ($P < 0.05$), to 180% after 10 mg/kg and to 280% of basal after 20 mg/kg at 75–100 min after injections ($P < 0.01$). In both brain areas, the effects of BMY-14802 on HVA were long-lasting: HVA levels remained elevated for over 5 h after 20 mg/kg BMY-14802 injections ($P < 0.01$).

After 5 or 10 mg/kg, BMY-14802 did not change dorsal raphe or hippocampal 5-HIAA concentrations. However, a significant decrease to 85% of basal in hippocampal 5-HIAA was observed after 20 mg/kg BMY-14802 ($P < 0.05$). This dose did not change dorsal raphe 5-HIAA levels (results not shown).

3.2. Effects of BMY-14802 on dorsal raphe and hippocampal 5-HT in the presence of WAY-100635

Systemic administration of the selective 5-HT_{1A} receptor antagonist, WAY-100635 (1.0 mg/kg, i.p.) administered 50 min before BMY-14802 (10 mg/kg, i.p.) completely antagonized the 5-HT decreases produced by BMY-14802 in dorsal raphe and hippocampus (Fig. 3). There was a significant difference ($P < 0.01$) between the two groups: WAY-100635 plus BMY-14802 versus BMY-14802 alone, from 150 min to 250 min after BMY-14802 injection (Fig. 3). The combination of WAY-100635 and BMY-14802 did not significantly change dorsal raphe or hippocampal 5-HT from baseline levels.

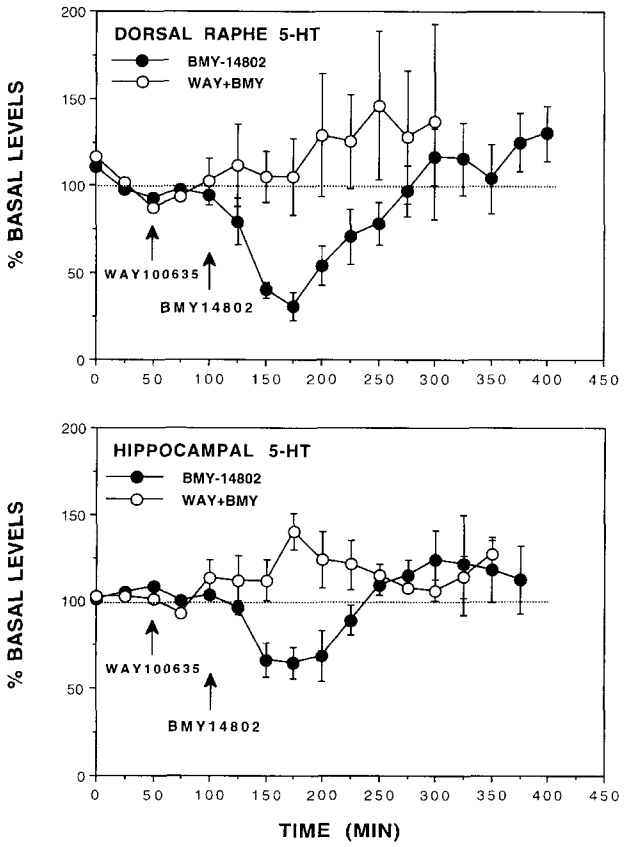

Fig. 3. Time-courses of the effects of BMY-18402 alone (10 mg/kg, i.p., injection at the arrow) and in presence of WAY-100635 (WAY, 1 mg/kg, i.p., injection at the arrow) on extracellular concentrations of 5-HT in dialysates from dorsal raphe (top) and ventral hippocampus (bottom). Rats were pretreated with WAY-100635, 50 min before BMY-14802. Each point represents the mean ± S.E.M. ($n = 4$). Significant differences ($P < 0.01$) in 5-HT levels were obtained between the two groups: WAY-100635 plus BMY-14802 versus BMY-14802 alone, from 150–250 min in the dorsal raphe and 150–200 min in the hippocampus (see text).

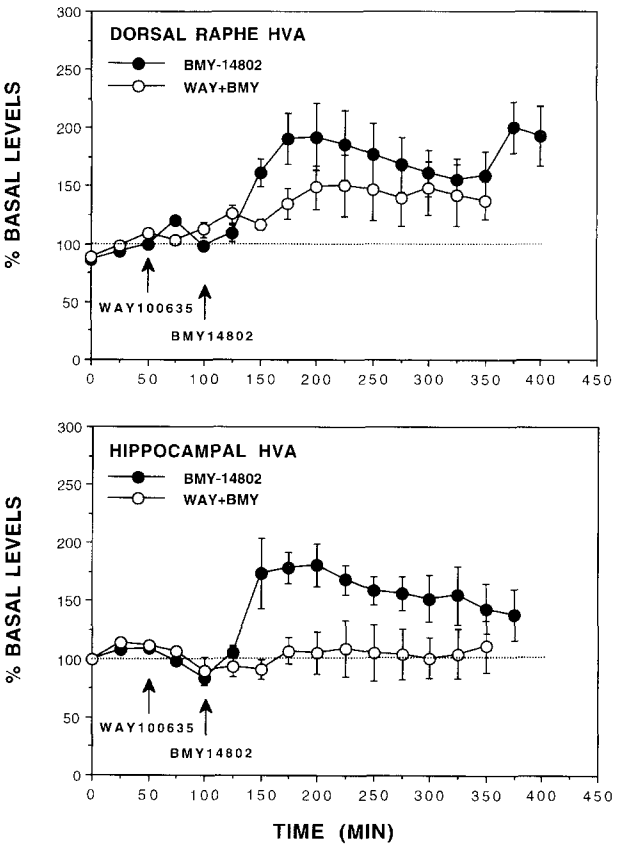

Fig. 4. Time-courses of the effects of BMY-14802 alone (10 mg/kg, i.p., injection at the arrow) and in presence of WAY-100635 (WAY, 1 mg/kg, i.p., injection at the arrow) on extracellular concentrations of HVA in dialysates from dorsal raphe (top) and ventral hippocampus (bottom). Rats were pretreated with WAY-100635, 50 min before BMY-14802. Each point represents the mean ± S.E.M. ($n = 4$). Significant differences in HVA levels ($P < 0.01$) were obtained between the two groups: WAY-100635 plus BMY-14802 versus BMY-14802 alone.

In addition, WAY-100635 significantly ($P < 0.01$) attenuated the HVA increase produced by 10 mg/kg BMY-14802 in the dorsal raphe and hippocampus (Fig. 4). The combination of WAY-100635 and BMY-14802 did not significantly change hippocampal HVA from baseline levels, but induced a small increase in dorsal raphe HVA at 75–100 min after administration ($P < 0.05$, Fig. 4). Administration of WAY 100635 alone, at doses up to 10 mg/kg, did not significantly change extracellular 5-HT, 5-HIAA or HVA concentrations in dorsal raphe or hippocampus (results not shown).

4. Discussion

The results obtained in the present study show that systemic BMY-14802 dose-dependently decreased extracellular 5-HT concentrations simultaneously in the dorsal

raphe and ventral hippocampus. Although BMY-14802 was originally identified as a potent σ antagonist with a behavioral profile of an atypical antipsychotic (Taylor et al., 1991), in vivo electrophysiological and behavioral studies indicated that BMY-14802 also has 5-HT_{1A} receptor agonist activity (VanderMaelen and Braselton, 1990; Bristow et al., 1991; Smith et al., 1992). To this end, systemic administration of BMY-14802 inhibited neuronal firing of 5-HT neurons in the dorsal raphe (VanderMaelen and Braselton, 1990) and induced a 5-HT syndrome, hypothermia and other behaviors consistent with the effects of 5-HT_{1A} receptor agonists in rats and mice (Bristow et al., 1991). In addition, behavioral studies assessing the potential anxiolytic efficacy of BMY-14802 demonstrated that BMY-14802 was active in the rat social interaction model and is similar to the clinically effective anxiolytic, buspirone (Smith et al., 1992).

Systemic injections of BMY-14802 markedly decreased dorsal raphe and hippocampal 5-HT concentrations. The decrease in hippocampal 5-HT release induced by BMY-14802 is consistent with previous experiments demonstrating a decrease in extracellular 5-HT concentrations in the rat ventral hippocampus following systemic injections of the 5-HT_{1A} receptor agonists, buspirone, gepirone, ipsapirone or 8-OH-DPAT (Sharp et al., 1989a; Nomikos et al., 1992; Matos et al., 1996). The decrease in dorsal raphe and hippocampal 5-HT release induced by BMY-14802 is due to activation of 5-HT_{1A} receptors localized on the soma and dendrites of serotonergic neurons in the midbrain raphe nuclei (dorsal and median). Interaction of 5-HT_{1A} receptor agonists with somatodendritic autoreceptors results in a decrease in cell firing and consequently impulse flow to terminal areas. This notion is supported by electrophysiological data showing that systemic or iontophoretic administration of buspirone, ipsapirone, or 8-OH-DPAT inhibited dorsal raphe serotonergic neuronal cell firing, suggesting that these receptors function as autoreceptors mediating cell firing and consequently terminal release of 5-HT (VanderMaelen et al., 1986; Sprouse and Aghajanian, 1987; Blier and DeMontigny, 1987). Furthermore, the dorsal raphe is an area extremely rich in serotonergic cell bodies an dendrites with a dearth in 5-HT terminals (Baraban and Aghajanian, 1981; Descarries et al., 1982; Pecci-Saavedra et al., 1986) and 5-HT release in this nuclei is dependent upon voltage activated sodium channels possibly located on the somatodendritic membranes (Matos et al., 1996). Taken together these data indicate that 5-HT release in the dorsal raphe is dependent upon action potential discharge.

Further evidence that the actions of BMY-14802 on somatodendritic and terminal 5-HT release is mediated by 5-HT_{1A} receptors is provided by our results with the selective 5-HT_{1A} receptor antagonist, WAY-100635. Pretreatment with WAY-100635 (1.0 mg/kg), completely antagonized the decreases in extracellular 5-HT in dorsal raphe and hippocampus following 10 mg/kg BMY-14802. These data are in agreement with previous reports that WAY-100635 antagonized the inhibition of dorsal raphe cell firing, the decrease in hippocampal extracellular 5-HT and the behavioral effects produced by 8-OH-DPAT (Gurling et al., 1994; Fletcher et al., 1994). The decreases in hippocampal 5-HT induced by 5-HT_{1A} receptor agonists are also blocked by non-selective β adrenoceptor/5-HT_{1A} receptors antagonists such as (−)-propranolol, pindolol or penbutolol (Sharp et al., 1989b; Hjorth and Sharp, 1993) and by the more specific 5-HT_{1A} receptor antagonist (S)-UH-301 (Nomikos et al., 1992). Taken together, our results strongly suggest that BMY-14802 decreases somatodendritic and hippocampal 5-HT release by a direct interaction at 5-HT_{1A} receptors localized in the somatodendritic membranes in the raphe nuclei (dorsal and median). However, since α_1 receptor antagonists decrease extracellular hippocampal 5-HT levels (Hjorth et al., 1995), it is possible that these receptors may play a role in the effects of BMY-14802 at higher doses.

Systemic administration of BMY-14802 produced a marked increase in extracellular concentrations of the dopamine metabolite, HVA. This observation is in agreement with studies showing that BMY-14802 increased dopamine synthesis, turnover, release and metabolism in striatum, frontal cortex and olfactory tubercle (Matthews et al., 1986; Rao et al., 1990). The HVA-increases produced by BMY-14802 are likely due to a direct effect on 5-HT_{1A} receptors since these effects were effectively antagonized by the specific 5-HT_{1A} receptor antagonist, WAY-100635. It is possible that there are 5-HT_{1A} receptors localized on dopaminergic terminals controlling dopamine release and metabolism. Several 5-HT_{1A} receptor agonists have been shown to increase levels of dopamine metabolites. For instance, systemic 8-OH-DPAT and buspirone increased extracellular and tissue concentrations of 3,4-dihydroxyphenyl acetic acid (DOPAC) and HVA in striatum (Nomikos et al., 1992; Cimino et al., 1983; McMillen et al., 1983) and buspirone increased HVA in dorsal raphe and hippocampus (Matos et al., 1996), indicating a functional interaction between the serotonergic and dopaminergic systems. In fact, Nomikos et al. (1992) have shown that the increase in hippocampal concentrations of DOPAC and HVA induced by 8-OH-DPAT were completely blocked by systemic pretreatment of the selective 5-HT_{1A} receptor antagonist (S)-UH-301. In view of the fact that 5-HT_{1A} receptor agonists increase hippocampal norepinephrine release (Done and Sharp, 1994) and that hippocampal DOPAC and presumably HVA arise from noradrenergic as well as dopaminergic neurons (Vahabzadeh and Fillenz, 1992), it is conceivable that there might be also a noradrenergic component to the HVA response. Interaction of dopamine D_1 or D_2 antagonists at the dopaminergic terminal, will also result in an increase in extracellular DOPAC and HVA (Zetterström et al., 1985). However, it is unlikely that the effects of BMY-14802 on HVA levels result from a direct interaction with dopamine

D_1 or D_2 receptors, since this compound does not significantly bind to these receptors.

In summary, our microdialysis data provide strong evidence that the putative antipsychotic, BMY-14802 acts as a 5-HT_{1A} receptor agonist in vivo, decreasing 5-HT release and increasing extracellular HVA in the rat dorsal raphe and hippocampus. BMY-14802 interacts with multiple receptor sites and its antipsychotic potential has been attributed to activity at σ receptors. Our present findings, together with the observations that BMY-14802 induces a behavioral profile indicative of a 5-HT_{1A} receptor agonist (Bristow et al., 1991), and that BMY-18402 is similar to buspirone in a behavior model for anxiolytic activity (Smith et al., 1992) now suggest that BMY-14802 also has anxiolytic potential.

Acknowledgements

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