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Studies on the role of 5-HT_{2C} and 5-HT_{2B} receptors in regulating generalised seizure threshold in rodents

Neil Upton *, Tania Stean, Derek Middlemiss, Tom Blackburn, Guy Kennett

Neurosciences Department, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, UK

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Abstract

The present studies were conducted to investigate the role of 5-HT_{2C} and 5-HT_{2B} receptors in the generation of pentylenetetrazol and electroshock-evoked seizures. The 5-$HT_{2C/2B}$ receptor-preferring agonist 1-(*m*-chlorophenyl)-piperazine (mCPP; 2.5–7 mg/kg i.p.) weakly elevated seizure threshold in the mouse (but not the rat) electroshock test and also provided appreciable protection against pentylenetetrazol-induced myoclonic and/or tonic seizures in mice and rats, an action that was inhibited by the 5-$HT_{2C/2B}$ receptor antagonist 5-methyl-1-(3-pyridylcarbomoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (SB-206553; 10–20 mg/kg p.o.). In contrast, the 5-HT_{2B} receptor agonist 1-[5-(2-thienylmethoxy)-1*H*-3-indoyl]propan-2-amine hydrochloride (BW-723C86; 3–30 mg/kg s.c.) had no effect on the threshold for generalised seizures in any of the models employed. These results indicate that the observed anticonvulsant effects of mCPP are likely to be mediated by activation of 5-HT_{2C} receptors. However, blockade of these receptors in mice (or rats) by SB-206553 (5–20 mg/kg p.o.) did not result in the reduced seizure threshold characteristic of mutant mice deficient of 5-HT_{2C} receptors, suggesting that in normal adult animals this receptor subtype may usually be subjected to only a low level of 5-hydroxytryptamine tone.

Keywords: 5-HT_{2C} receptor; 5-HT_{2B} receptor; SB-206553; BW-723C86; *m*-Chlorophenylpiperazine; Seizure

1. Introduction

There is growing evidence that serotonergic neurotransmission modulates a wide variety of experimentally induced seizures and is involved in the enhanced seizure susceptibility observed in some genetically epilepsy-prone rodents (Kilian and Frey, 1973; Buterbaugh, 1978; Przegalinski, 1985; Hiramatsu et al., 1987; Dailey et al., 1992). Generally, agents that elevate extracellular serotonin (5-hydroxytryptamine, 5-HT) levels, such as 5-hydroxytryptophan and 5-HT reuptake blockers, inhibit both limbic and generalised seizures (De La Torre et al., 1970; Löscher et al., 1984; Prendiville and Gale, 1993; Yan et al., 1994). Conversely, depletion of brain 5-HT lowers the threshold to audiogenically, chemically and electrically evoked convulsions (De La Torre et al., 1970; Browning et al., 1978; Statnick et al., 1996).

Little is known about the role of 5-HT receptor subtypes in the modulation of seizure activity. Recent experiments using pharmacological probes have implicated 5-HT_2 receptors in the development of amygdala-kindled limbic seizures (Wada et al., 1997) and the expression of electrically induced generalised seizures (Przegalinski et al., 1994) in rodents. The possible involvement of 5-HT_{2C} receptors has been suggested by the finding that genetically-modified mice lacking this receptor subtype undergo spontaneous generalised seizures and exhibit a reduced seizure threshold (Tecott et al., 1995).

In order to further delineate the role of 5-HT_{2C} receptors in seizure generation, we have determined the effects of the 5-$HT_{2C/2B}$ receptor-preferring agonist 1-(*m*-chlorophenyl)-piperazine (mCPP) (Kennett, 1993) and the 5-$HT_{2C/2B}$ receptor antagonist 5-methyl-1-(3-pyridylcarbomoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole (SB-206553) (Kennett et al., 1996b) in established models of electrically and chemically induced generalised seizures (Upton, 1994; Upton et al., 1997). For comparative pur-

* Corresponding author. Tel.: +44-1279-622108; Fax: +44-1279-622211.

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poses, the 5-HT_{2B} receptor agonist 1-[5-(2-thienylmethoxy)-1*H*-3-indoyl]propan-2-amine hydrochloride (BW-723C86), which has roughly an order of magnitude selectivity for this receptor over other 5-HT receptor subtypes (Kennett et al., 1997a), was also studied. Blockade of 5-HT_{2C} receptors in adult mice (or rats) did not result in the increased sensitivity to generalised convulsions characteristic of mutant mice deficient of this receptor subtype (Tecott et al., 1995).

2. Materials and methods

2.1. Animals

Animal husbandry and experimentation was conducted in compliance with the Home Office Guidance on the operation of the UK Animals (Scientific Procedures) Act 1986, and was reviewed and approved by the SmithKline Beecham Procedures Review Panel.

Male CD1 mice housed in maximum groups of 20 and male Sprague–Dawley rats housed in groups of 6–10 were supplied by Charles River, UK. Animals were maintained on a 12 h light/dark cycle with lights on at 0700 h and food (Combined Rat and Mouse Diet, Special Diet Services, Witham, UK) and water were available ad libitum.

In all experiments, seizure thresholds were determined between 1000 h and 1500 h in time-matched vehicle and drug-treated groups.

2.2. Maximal electroshock seizure threshold test

The threshold for electroshock-induced tonic hindlimb extensor seizures in male mice (CD1 strain, 25–30 g) and rats (Sprague–Dawley strain, 70–130 g) was determined using a Hugo Sachs Elektronic stimulator which delivered a constant current (0.1 s (mice) or 0.3 s (rats) duration, 50 Hz, sinewave form, fully adjustable between 1–300 mA) via corneal electrodes. The stimulus intensity was varied (from the typical baseline current of 14 or 25 mA in mice and rats, respectively) by an 'up-and-down' method of shock titration using current steps of 2 (mice) or 5 (rats) mA (for details, see Upton et al., 1997). Hindlimb extension was scored as absent or present. The data generated from treatment groups of 12–15 mice and 10–14 rats were used to calculate the CC_{50} value (current producing maximal seizures in 50% of animals) ± S.E.M according to the method of Kimball et al. (1957).

2.3. Intravenous pentylenetetrazol seizure threshold

Lightly restrained male mice (CD1, 25–30 g) or rats (Sprague–Dawley, 160–240 g) were infused with pentylenetetrazol (8 mg/ml, 0.5 ml/min (mice) or 20 mg/ml, 1 ml/min (rats)) via a butterfly cannula placed in a superficial tail vein. Latencies (t, s) to onset of myoclonic (defined as one or more isolated whole body jerks) and tonic forelimb and/or hindlimb extension seizures were then recorded up to a cut-off of 2 min. Using these infusion parameters tonic hindlimb extension seizures were not reliably seen in rats and therefore this end-point was not recorded in this species. The mean ± S.E.M. threshold doses of pentylenetetrazol required to produce the different seizure types were determined for treatment groups of 11–12 mice or rats. Threshold doses (mg/kg) were calculated according to the following formula: conc. of pentylenetetrazol (mg/ml) × time (s) × flow rate (ml/s)/body weight (kg).

2.4. Drugs and administration

BW-723C86 (1-[5-(2-thienylmethoxy)-1*H*-3-indoyl]propan-2-amine hydrochloride), SB-206553 (5-methyl-1-(3-pyridylcarbomoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole) and FG-7142 (*N*-methyl-β-carboline-3-carboxamide) were synthesised in the Medicinal Chemistry Department at SmithKline Beecham, Harlow, UK. Picrotoxin, 4-aminopyridine, carbamazepine, mCPP (1-(*m*-chlorophenyl)-piperazine) and pentylenetetrazol were obtained from Sigma (Poole, UK) and diazepam from Courtin and Warner (Lewes, UK).

Picrotoxin, 4-aminopyridine, mCPP, BW-723C86 and pentylenetetrazol were dissolved in 0.9% saline and SB-206553 was finely suspended in 1% methyl cellulose (Fisons, Loughborough, UK) in water. FG-7142 was dispersed in saline + Tween 80. Treatments were administered orally, subcutaneously or intraperitoneally in a dose volume of 1 ml/kg in rats and 10 ml/kg in mice, with the exception of pentylenetetrazol, which was infused intravenously. The doses (and pretest times) chosen for mCPP, BW-723C86 and SB-206553 have previously been shown to produce 5-HT_{2C} and/or 5-HT_{2B} receptor-mediated central effects (Kennett et al., 1996a,b, 1997a).

2.5. Statistical analysis

Significant effects ($P < 0.05$) of drugs on the threshold for maximal electroshock seizures were determined by comparison of the potency ratios of the CC_{50} values of the drug and vehicle-treated groups by the method of Litchfield and Wilcoxon (1949). In the intravenous pentylenetetrazol infusion test, the ability of SB-206553 to antagonise mCPP-induced effects and significant changes between drug and vehicle-treated controls were assessed using Kruskal–Wallis ANOVA followed by Mann–Whitney *U*-test. FG-7142, 4-aminopyridine and diazepam-in-

Table 1
Effect of BW-723C86, mCPP, SB-206553 and standards on the threshold for maximal (tonic hindlimb extension) electroshock seizures in mice and rats

Treatment	Dose (mg/kg) and route	Pre-test time (min)	Seizure threshold (mA)	
			Mouse	Rat
Vehicle		30[a]/60[b]	15.0 ± 0.7	25.0 ± 1.1
Carbamazepine	5 p.o.	30/60	19.6 ± 0.7	32.5 ± 2.3[e]
	10 p.o.	30/60	25.6 ± 0.7[e]	80.0 ± 6.0[e]
	15 p.o.	30/60	32.7 ± 0.9[e]	168.3 ± 2.8[e]
Vehicle		30	16.7 ± 0.6	
4-Aminopyridine	0.8 i.p.	30	13.6 ± 0.7[e]	
Vehicle		30		18.9 ± 0.9
Picrotoxin	2 i.p.	30		15.0 ± 1.1[d]
Vehicle		20	14.2 ± 1.0	25.0 ± 2.0
BW-723C86	3 s.c.	20	14.0 ± 0.4	22.5 ± 1.1
	10 s.c.	20	13.0 ± 0.5	22.5 ± 2.3
	30 s.c.	20	14.0 ± 0.4	20.8 ± 1.9
Vehicle		20	14.0 ± 1.2	23.3 ± 3.6
mCPP	1 i.p.	20	14.3 ± 0.4	24.2 ± 1.0
	2.5 i.p.	20	17.0 ± 0.5[c]	25.4 ± 1.0
	7 i.p.	20	15.7 ± 1.2	27.5 ± 4.2
Vehicle		60	13.9 ± 0.7	22.5 ± 1.3
SB-206553	5 p.o.	60	12.4 ± 1.3	25.8 ± 3.9
	10 p.o.	60	14.7 ± 0.7	25.8 ± 1.9
	20 p.o.	60	13.0 ± 0.5	26.7 ± 1.7

Seizure thresholds were evaluated as CC_{50} (±S.E.M.) values in groups of 12–15 mice and 10–14 rats. [a]Mouse, [b]rat. [c]$P < 0.05$, [d]$P < 0.01$, [e]$P < 0.001$, compared to corresponding vehicle-treated controls according to Litchfield and Wilcoxon (1949).

duced changes relative to vehicle-treated controls were evaluated using Mann–Whitney *U*-test.

3. Results

At the doses tested, mice or rats receiving BW-723C86 or SB-206553 did not show any overt behavioural effects whereas those administered mCPP at the highest dose (7 mg/kg i.p.) only, exhibited reduced locomotion prior to seizure induction.

3.1. Mouse and rat maximal electroshock seizure threshold tests

As expected, the established anticonvulsant agent carbamazepine (5–15 mg/kg p.o.) dose-dependently elevated the threshold for electroshock-induced tonic hindlimb extension seizures while in contrast, the known proconvulsant compounds 4-aminopyridine (0.8 mg/kg i.p.) and picrotoxin (2 mg/kg i.p.) significantly ($P < 0.01$–$P < 0.001$) lowered seizure threshold in the mouse and/or rat maximal electroshock seizure threshold tests (Table 1).

Table 2
Effect of SB-206553 on the anticonvulsant activity of mCPP in the mouse maximal electroshock seizure threshold test

Pre-treatment (p.o., 1 h pre-test)	Treatment (i.p., 20 min pre-test)	Seizure threshold (mA)
Vehicle	Vehicle	12.4 ± 0.6
SB-206553 5 mg/kg	Vehicle	11.9 ± 0.4
SB-206553 10 mg/kg	Vehicle	11.9 ± 0.7
SB-206553 20 mg/kg	Vehicle	14.1 ± 0.7
Vehicle	mCPP 2.5 mg/kg	17.3 ± 1.9[a]
SB-206553 5 mg/kg	mCPP 2.5 mg/kg	15.0 ± 0.7[b,c]
SB-206553 10 mg/kg	mCPP 2.5 mg/kg	14.4 ± 1.0[c]
SB-206553 20 mg/kg	mCPP 2.5 mg/kg	15.0 ± 0.7[b,c]

Seizure thresholds were evaluated as CC_{50} (±S.E.M.) values in groups of 14–15 mice. [a]$P < 0.05$, [b]$P < 0.01$, compared to vehicle + vehicle-treated control group and [c]non-significant, compared to vehicle + mCPP-treated group according to Litchfield and Wilcoxon (1949).

Table 3
Effect of BW-723C86, SB-206553 and standards in the mouse pentylenetetrazol (PTZ) infusion model

Treatment	Dose (mg/kg) and route	Pre-test time (min)	Mean ± S.E.M. dose of PTZ (mg/kg i.v.)		
			Myoclonus	Forelimb tonus	Hindlimb tonus
Vehicle		30	26.6 ± 0.8	37.3 ± 3.0	40.6 ± 3.2
4-Aminopyridine	1 i.p.	30	21.5 ± 0.9[b]	28.2 ± 1.8[a]	30.7 ± 1.8[b]
Vehicle		60	32.9 ± 1.6	44.2 ± 2.2	48.6 ± 2.7
Diazepam	2.5 p.o.	60	58.1 ± 3.9[b]	86.8 ± 4.6[b]	95.6 ± 8.6[b]
Vehicle		60	36.0 ± 2.1	50.6 ± 2.2	56.8 ± 2.6
SB-206553	10 p.o.	60	44.5 ± 2.1[b]	53.7 ± 2.4	58.7 ± 2.6
	20 p.o.	60	41.8 ± 2.3	53.3 ± 2.4	57.0 ± 2.5
$H(df = 2)$ values			8.37, $P < 0.05$	1.00, NS	0.19, NS
Vehicle		20	34.6 ± 2.1	42.2 ± 2.5	46.2 ± 2.5
BW-723C86	3 s.c.	20	28.5 ± 1.5	39.8 ± 3.6	46.4 ± 5.9
	10 s.c.	20	30.3 ± 1.5	43.0 ± 2.5	49.0 ± 3.1
	30 s.c.	20	34.3 ± 0.8	52.0 ± 4.3	58.0 ± 5.7
$H(df = 3)$ values			7.61, NS	6.93, NS	7.01, NS

The thresholds for myoclonic and forelimb and hindlimb tonic seizures were determined following timed i.v. infusion of PTZ in groups of 11–12 mice. Data represent the mean (±S.E.M.) doses of PTZ required to induce the various seizure types. [a]$P < 0.05$, [b]$P < 0.01$, compared to corresponding vehicle-treated controls by (two-tailed) Mann–Whitney *U*-test following significant Kruskal–Wallis ANOVA (*H*-values shown, NS: non-significant) for SB-206553 and BW-723C86, or by Mann–Whitney *U*-test for 4-aminopyridine and diazepam.

Unlike the standards, BW-723C86 (3–30 mg/kg s.c.) and SB-206553 (5–20 mg/kg p.o.) had no effect on seizure threshold in either species (Tables 1 and 2). mCPP (1–7 mg/kg i.p.) did not change the current required to induce tonic extension in rats but in the mouse model produced a weak increase (21%; $P < 0.05$) in seizure threshold at the dose of 2.5 mg/kg i.p. (Table 1). As shown in Table 2, a comparable anticonvulsant effect of mCPP (2.5 mg/kg i.p.) was partially inhibited (47–59%) by SB-206553 (5–20 mg/kg p.o.), although this effect failed to reach significance ($P > 0.05$) at any of the doses tested.

3.2. Mouse and rat pentylenetetrazol infusion tests

Diazepam (2.5 or 7.5 mg/kg p.o.) significantly ($P < 0.01$) increased the doses of pentylenetetrazol required to induce myoclonic and tonic extension seizures in mice (Table 3) and rats (Table 4) whereas the proconvulsant

Table 4
Effect of BW-723C86, SB-206553 and standards in the rat pentylenetetrazol (PTZ) infusion model

Treatment	Dose (mg/kg) and route	Pre-test time (min)	Mean ± S.E.M. dose of PTZ (mg/kg i.v.)	
			Myoclonus	Forelimb tonus
Vehicle		15	29.1 ± 0.8	45.5 ± 1.9
FG-7142	30 i.p.	15	22.3 ± 0.9[a]	34.1 ± 1.9[a]
Vehicle		60	35.9 ± 1.1	48.2 ± 1.2
Diazepam	7.5 p.o.	60	46.8 ± 2.4[a]	69.6 ± 2.6[a]
SB-206553	3 p.o.	60	35.3 ± 1.3	59.4 ± 2.9[a]
	10 p.o.	60	36.6 ± 1.2	53.8 ± 2.3
	30 p.o.	60	35.2 ± 1.2	47.8 ± 1.9
	100 p.o.	60	34.8 ± 1.3	49.8 ± 2.0
$H(df = 5)$ values			19.23, $P < 0.01$	30.97, $P < 0.001$
Vehicle		20	31.7 ± 1.0	41.6 ± 0.6
BW-723C86	3 s.c.	20	31.7 ± 1.0	42.5 ± 1.2
	10 s.c.	20	33.4 ± 1.0	43.9 ± 0.7
	30 s.c.	20	34.3 ± 0.9	45.3 ± 1.1
$H(df = 3)$ values			5.36, NS	6.98, NS

The thresholds for myoclonic and forelimb tonic seizures were determined following timed i.v. infusion of PTZ in groups of 11–12 rats. Data represent the mean (±S.E.M.) doses of PTZ required to induce the various seizure types. [a]$P < 0.01$, compared to corresponding vehicle-treated controls by (two-tailed) Mann–Whitney *U*-test following significant Kruskal–Wallis ANOVA (*H*-values shown, NS: non-significant) for diazepam, SB-206553 and BW-723C86, or by Mann–Whitney *U*-test for FG-7142.

agents FG-7142 (30 mg/kg i.p.) and 4-aminopyridine (1 mg/kg i.p.) had the opposite effect and significantly ($P < 0.05$–$P < 0.01$) reduced the threshold for both seizure types (Tables 3 and 4). BW-723C86 (3–30 mg/kg s.c.) had no effect in either species (Tables 3 and 4) unlike mCPP which caused a significant ($P < 0.05$–$P < 0.01$) increase in the threshold for tonic seizures at doses of 1–7 mg/kg i.p. in mice (Fig. 1a) and rats (Fig. 2a). The magnitude of this anticonvulsant effect appeared to be greater in mice than in rats although activity declined at the highest dose tested (7 mg/kg i.p.) in the former species. In addition, mCPP (2.5 and 7 mg/kg i.p.) produced significant ($P < 0.01$) protection against myoclonic seizures in mice (Fig. 1a) but not in rats (Fig. 2a).

SB-206553 (10 and 20 mg/kg p.o. in mice; 3–100 mg/kg p.o. in rats) had little effect in the pentylenetetrazol infusion tests other than producing a weak increase in myoclonic seizure threshold in mice (24% at 10 mg/kg p.o., $P < 0.01$; Table 3) and forelimb tonic seizure threshold in rats (23% at 3 mg/kg p.o., $P < 0.01$; Table 4) at a

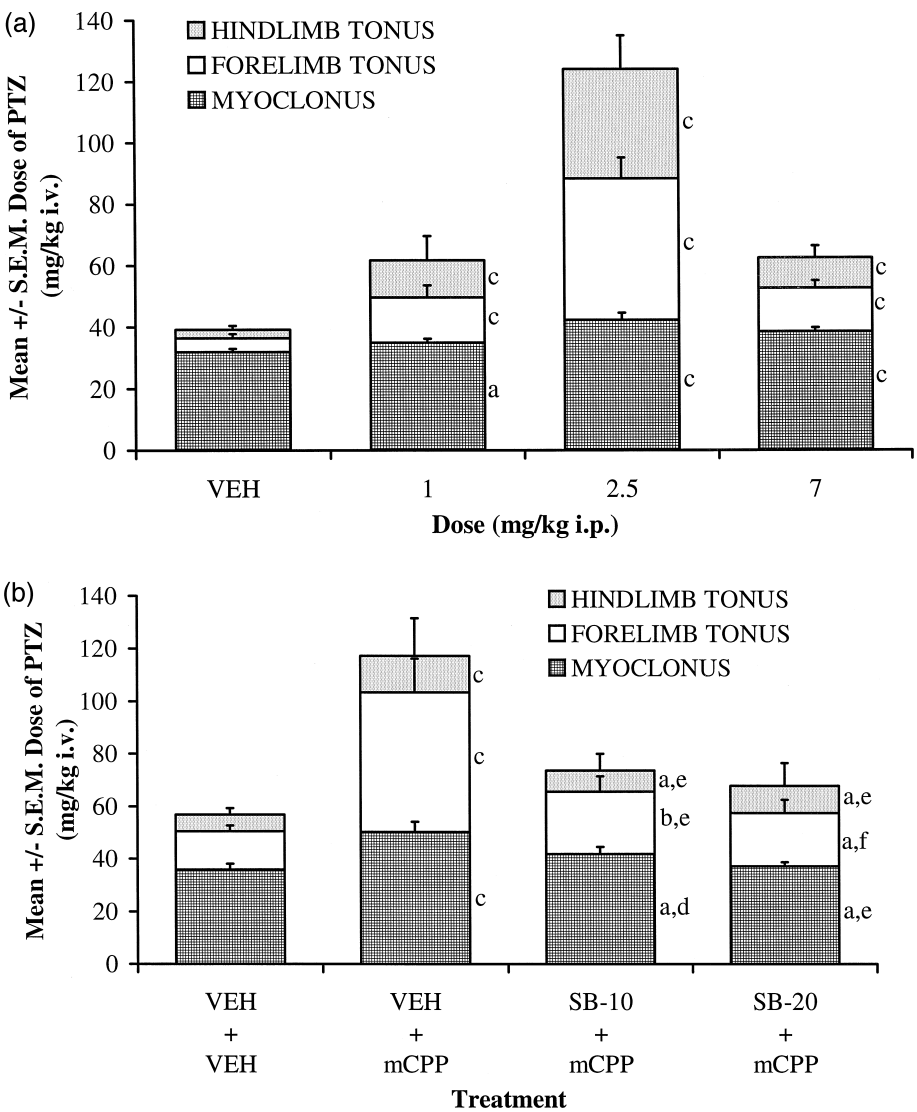

Fig. 1. (a) Anticonvulsant effect of mCPP (1–7 mg/kg i.p., 20 min pre-test) in the mouse i.v. pentylenetetrazol (PTZ) infusion test. Data are the mean (±S.E.M.) doses of PTZ required to induce myoclonic and tonic forelimb and hindlimb extension seizures in groups of 11–12 mice. [a]Non-significant, [c]$P < 0.01$, compared to vehicle (VEH)-treated controls by (two-tailed) Mann–Whitney *U*-test following significant Kruskal–Wallis ANOVA (myoclonic seizures; $H(df = 3) = 16.91$, $P < 0.001$: forelimb tonus; $H(df = 3) = 36.11$, $P < 0.001$: hindlimb tonus; $H(df = 3) = 32.21$, $P < 0.001$). (b) Antagonism of the anticonvulsant effect of mCPP (2.5 mg/kg i.p., 20 min pre-test) by SB-206553 (SB; 10–20 mg/kg p.o., 1 h pre-test). Data are the mean (±S.E.M.) doses of PTZ required to induce myoclonic and tonic forelimb and hindlimb extension seizures in groups of 11–12 mice. [a]Non-significant, [b]$P < 0.05$, [c]$P < 0.01$, compared to vehicle (VEH) controls and [d]non-significant, [e]$P < 0.05$, [f]$P < 0.01$, compared to mCPP alone by (two-tailed) Mann–Whitney *U*-test following significant Kruskal–Wallis ANOVA (myoclonic seizures; $H(df = 3) = 10.96$, $P < 0.01$: forelimb tonus; $H(df = 3) = 16.34$, $P < 0.001$: hindlimb tonus; $H(df = 3) = 13.91$, $P < 0.01$).

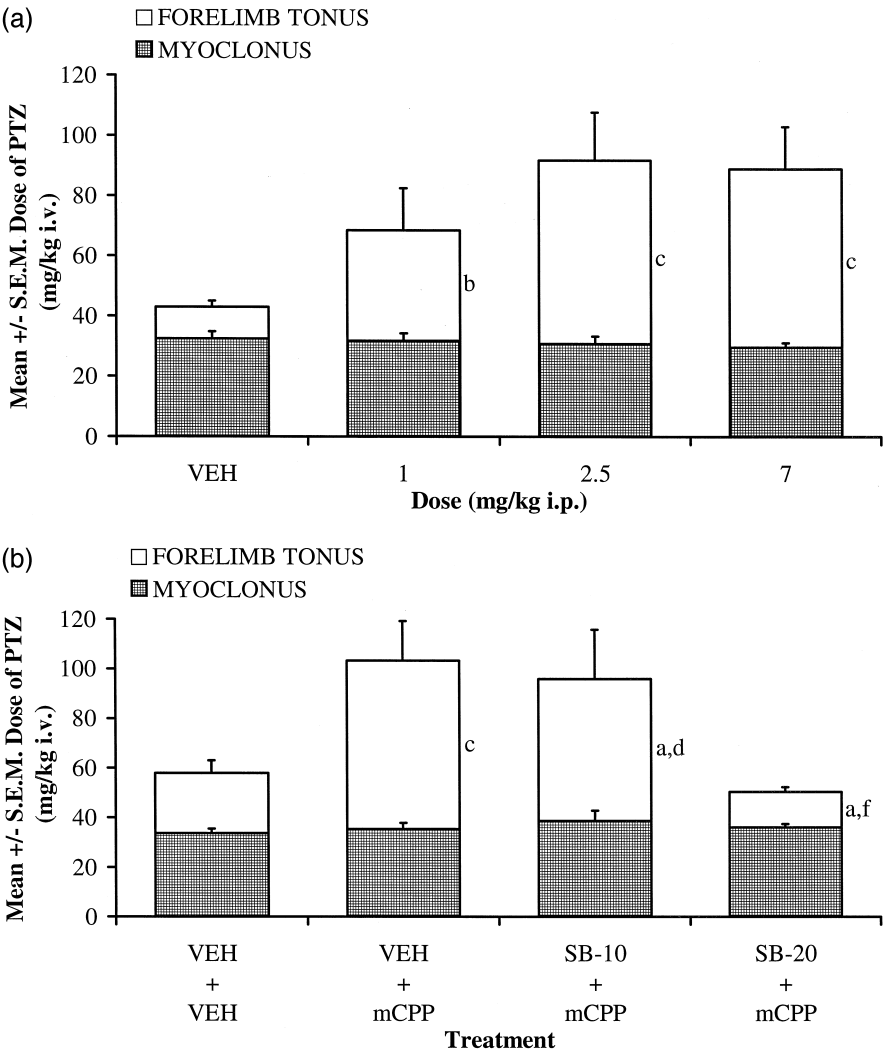

Fig. 2. (a) Anticonvulsant effect of mCPP (1–7 mg/kg i.p., 20 min pre-test) in the rat i.v. pentylenetetrazol (PTZ) infusion test. Data are the mean (±S.E.M.) doses of PTZ required to induce myoclonic and tonic forelimb extension seizures in groups of 11–12 rats. [b]$P < 0.05$, [c]$P < 0.01$, compared to vehicle (VEH)-treated controls by (two-tailed) Mann–Whitney *U*-test following significant Kruskal–Wallis ANOVA (myoclonic seizures; $H(df = 3) = 4.01$, non-significant: forelimb tonus; $H(df = 3) = 14.26$, $P < 0.01$). (b) Antagonism of the anticonvulsant effect of mCPP (2.5 mg/kg i.p., 20 min pre-test) by SB-206553 (SB; 10–20 mg/kg p.o., 1 h pre-test). Data are the mean (±S.E.M.) doses of PTZ required to induce myoclonic and tonic forelimb extension seizures in groups of 11–12 rats. [a]Non-significant, [c]$P < 0.01$, compared to vehicle (VEH) controls and [d]non-significant, [f]$P < 0.01$, compared to mCPP alone by (two-tailed) Mann–Whitney *U*-test following significant Kruskal–Wallis ANOVA (forelimb tonus; $H(df = 3) = 9.43$, $P < 0.05$).

single dose. However, SB-206553 (20 mg/kg p.o.) was able to completely inhibit the protective action of mCPP (2.5 mg/kg i.p.) against pentylenetetrazol-induced myoclonic and/or tonic seizures in both mice (Fig. 1b) and rats (Fig. 2b).

4. Discussion

The pentylenetetrazol infusion and maximal electroshock seizure threshold tests employed in the present studies were selected for their sensitivity to both known anticonvulsant (e.g., carbamazepine, diazepam) and proconvulsant (e.g., picrotoxin, 4-aminopyridine, FG-7142) agents and also because they evoke several different types of generalised convulsions (Löscher and Schmidt, 1988; Upton, 1994). In these mouse and/or rat models, the 5-HT_{2B} receptor agonist BW-723C86 (Kennett et al., 1997a) had no effect on the threshold for myoclonic, forelimb tonic (pentylenetetrazol-induced) or hindlimb tonic (pentylenetetrazol or electroshock-induced) seizures. The compound was tested at doses (3–30 mg/kg s.c.) shown previously to evoke central 5-HT_{2B} receptor-mediated hyperphagia (Kennett et al., 1997a) and anxiolysis (Kennett et al., 1996a) in rats. The present findings are in accord with the observation that the selective 5-HT_{2B} receptor antagonist 6-chloro-5-methyl-1-(5-quinolylcarbamoyl)indoline (SB-215505; 1–10 mg/kg p.o.) does not

alter seizure threshold in the rat pentylenetetrazol infusion test (data not shown). In contrast, the 5-$HT_{2C/2B}$ receptor-preferring agonist mCPP (Kennett, 1993) weakly elevated seizure threshold in the mouse (but not the rat) maximal electroshock seizure threshold test and also provided appreciable protection against pentylenetetrazol-induced myoclonic and tonic seizures in mice and forelimb tonic seizures in rats. Taken together, the findings with BW-723C86 and mCPP suggest that the anticonvulsant properties of the latter agent are most likely to be attributable to an agonist action at 5-HT_{2C} receptors. This idea is supported by the observation that the 5-$HT_{2C/2B}$ receptor antagonist SB-206553 (Kennett et al., 1996b) was able to completely inhibit the anticonvulsant effects of mCPP (2.5 mg/kg i.p.) in the mouse and rat pentylenetetrazol infusion models at a dose (20 mg/kg p.o.) reported to antagonise other 5-HT_{2C} receptor-mediated functions in vivo (Kennett et al., 1996b).

The ability of mCPP to prevent tonic extension in mice and rats indicates that 5-HT_{2C} receptors may play a role in regulating seizure spread. In mice, mCPP also inhibits myoclonus suggesting an additional role for 5-HT_{2C} receptors in this species of raising seizure threshold (Piredda et al., 1985; Löscher and Schmidt, 1988). Interestingly, the level of anticonvulsant activity produced by mCPP against all seizure types in the mouse pentylenetetrazol infusion test was observed to diminish at the highest dose tested. It is presently unclear whether this decline is related to an action at 5-$HT_{2C/2B}$ receptors or is due to the emergence of effects at other receptor subtypes.

Although activation of 5-HT_{2C} receptors appeared to result in an anticonvulsant action, SB-206553 alone did not lower the threshold to myoclonus, forelimb and/or hindlimb tonus in mice or rats thereby indicating that blockade of this receptor subtype was not associated with enhanced susceptibility to generalised seizures. This finding is consistent with experiments demonstrating that the highly selective 5-HT_{2C} receptor antagonist SB-242084 did not produce proconvulsant activity in the rat maximal electroshock seizure threshold test even after administration at a very high acute dose (30 mg/kg p.o.) (Kennett et al., 1997b).

The inability of 5-HT_{2C} receptor antagonists to reduce seizure threshold in adult rodents contrasts with the observed characteristics of mutant mice lacking the 5-HT_{2C} receptor (Tecott et al., 1995). The mutant mice undergo spontaneous tonic-clonic convulsions and by 2–3 months of age exhibit enhanced susceptibility to pentylenetetrazol and audiogenic-induced seizures (Tecott et al., 1995; Brennan et al., 1997). The present results suggest that the epileptic phenotype exhibited by 5-HT_{2C} receptor-deficient mice may be secondary to developmental or neuroadaptive changes in the brain.

The failure of BW-723C86 to modulate pentylenetetrazol or electroshock-induced myoclonic or tonic extensor convulsions, implies that 5-HT_{2B} receptors are not directly involved in propagating these types of generalised seizures. Activation of 5-HT_{2C} receptors using agents such as mCPP produces an anticonvulsant profile in the pentylenetetrazol and maximal electroshock seizure threshold models indicating that this receptor subtype contributes mainly to the spread of generalised seizures in mice and rats but may also play a role in their induction in the former species. However, blockade of these receptors is not associated with a lowering of seizure threshold suggesting that the 5-HT_{2C} receptors implicated in the regulation of seizure generation and spread may normally be subjected to only a low level of 5-HT tone.

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