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Actions of Buspirone in a Putative Model of Anxiety in the Mouse

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Abstract—In a two-compartment box divided into a dark area and a brightly illuminated white area, mice taken from a dark environment showed aversion to the light and exhibited preference for exploratory rearings and line crossings in the black area. The peripheral administration of buspirone, and its injection into the dorsal raphe nucleus, lead to an increased time spent in the white area associated with enhanced exploratory behaviour with a decreased incidence of rearings and line crossings in the black section. In contrast, the injection of 5-hydroxytryptamine and 2-methyl-5-hydroxytryptamine into the dorsal raphe nucleus increased exploratory behaviour in the black section with decreased activity in the white area: the effects of 2-methyl-5-hydroxytryptamine were antagonized by buspirone administered peripherally. Ritanserin, methysergide, metergoline and cyproheptadine failed, in non-sedative doses, to influence exploratory behaviour in the two-compartment system and ritanserin and methysergide also failed to antagonize the effects caused by 2-methyl-5-hydroxytryptamine. It is concluded that in the mouse model the ability of buspirone to reduce the aversive response to a brightly illuminated area may reflect an anxiolytic action, that the dorsal raphe nucleus may be an important locus of action, and that the effects of buspirone may reflect an interaction at 5-hydroxytryptamine receptors.

Buspirone is a pyrimidinylpiperazine derivative, unrelated to the benzodiazepines but with an anxiolytic action in the clinic (Goldberg & Finnerty 1979; Feighner et al 1982; Newton et al 1982; Rickels et al 1982; Wheatley 1982). The consistent clinical profile of buspirone as an antianxiety agent contrasts with an inconsistent action in animal models of anxiety. Thus, in some studies buspirone has been shown to have anxiolytic effects in conflict tests in rats and primates, but in different dose ranges or with markedly differing efficacies (Riblet et al 1982; Geller & Hartmann 1982; Oakley & Jones 1983; Taylor et al 1984; Weissman et al 1984; Barrett et al 1984; Merlo Pich & Samanin 1986) and not at all in others (Goldberg et al 1983; Gardner 1986). In the rat social interaction test buspirone had a variable effect dependent on light intensity (File 1984) or failed (Gardner & Guy 1985) to cause an anxiolytic action. Buspirone was ineffective in the staircase test in the mouse (Pollard & Howard 1986) whereas it exhibited anxiolytic action in a conflict test in the pigeon (Witkin & Barrett 1986).

When buspirone is effective, its mechanism and site of action is uncertain, but may involve an interaction with 5-hydroxytryptamine (5-HT) systems (Dourish et al 1986; Gardner 1986; Mennini et al 1986; Eison et al 1986; Chopin & Briley 1987; Traber & Glaser 1987). In the present study we assess the action of buspirone following its peripheral and intracerebral injection in a putative model of anxiety in the mouse, compare its activity with that of 5-HT receptor antagonists, and determine an ability to antagonize the effects of 2-methyl-5-HT.

Methods

Male albino mice, 25–35 g, were used. 10 mice were normally housed in each cage and given free access to food and water. The mice were kept on a 12 h light/dark cycle with lights off at 10.00 h.

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Behavioural studies

The method used for the detection of changes in anxiety was a modification of the test described by Crawley (1981). An open-topped box (45 × 27 × 27 cm high) was partitioned (with a connecting door, 7·5 × 7·5 cm, located at floor level) into two compartments, two fifths painted black illuminated under a dim red light (60W) (Lux 0) and the remainder of the box painted white and brightly illuminated with a 60W (Lux 400) light source. The temperature in each compartment was 22·4°C. The floor area was lined into 9 cm squares. The test was conducted between 1300 and 1800 h in a quiet, darkened room illuminated with red light only. Animals were taken in a dark container from a dark holding room to the dark testing room. 45 min after adaptation to the test room, mice that had received drug or vehicle injections were placed individually into the centre of the white area and their behaviour observed over a 5 min period by remote video recording. Four behavioural parameters were noted (a) the % time spent in each compartment (b) the number of transitions between the black and white chambers (c) the number of exploratory rearings and (d) the number of line crossings in the black and white areas.

The experimental design was to use animals in treatment groups of 5 and vehicle controls were run on each day of testing. It is emphasized that each animal was used on only one occasion. Results were analysed using Single-Factor Analysis of Variance followed, where appropriate, by Dunnett's procedure for comparing all treatments with control.

Stereotaxic surgery and intracerebral injection

Mice were anaesthetized with chloral hydrate (450 mg kg^{-1} i.p.) and placed in a Kopf stereotaxic frame using rat ear and incisor bars, the incisor bar being set at zero. Guide cannulae constructed from stainless steel tubing (0·64 mm diameter) held in perspex blocks were implanted using standard stereotaxic techniques and secured to the skull using a mixture of dental acrylic cement plus cyanoacrylate adhesive. The guide cannulae were kept patent by stylets extend-

ing to the tips of the guides. Animals were used 14 to 18 days after cannulation and on one occasion only. Mice were manually restrained and the stylets replaced by injection units (0·3 mm diameter) and drug or vehicle injected in a volume of 0·25 μL into the central area of the dorsal raphe nucleus (Ant. 0·5, Vert. 3·1, Lat. 0·0) (Atlas of Slotnick & Leonard 1975, was used as a guide) over a 5s period using Hamilton syringes, the units remaining in a position for a further 55s period before being withdrawn and the stylets replaced.

Histological analyses

On completion of the experiments the brains were removed and the site of injection determined in all animals using frozen tissue, the termination of the injection track clearly indicating the site of drug or vehicle deposition (Fig. 1).

Drugs

5-Hydroxytryptamine bimaleinate (Sigma), 2-methyl-5-hydroxytryptamine hydrogen maleinate (Glaxo), buspirone HCl (Bristol-Myers), methysergide maleate (Sandoz) and cyproheptadine HCl (Merck, Sharp and Dohme) were dissolved in distilled water. Metergoline (Sandoz) was prepared in the minimum quantity of ascorbic acid and ritanserin (Janssen) in the minimum quantity of acetic acid, both agents being prepared to volume with distilled water. Drugs given peripherally were administered intraperitoneally in a volume of 1 mL/100 g. All doses are expressed as the base.

Results

General observations

When assessed in the black and white test box system, non-drug-treated naive mice demonstrated an aversion to the white environment. Whilst the white area is larger than the black, mice spent approximately equal time in each section, demonstrated a greater number of rearings in the black (42·4 ± 3·9/5 min) compared with the white section (17·4 ± 1·8/5 min) and showed a trend to an increase in the line crossings in the black (52·5 ± 5·1/5 min) compared with the white section (42·0 ± 4·3/5 min) (Fig. 2, similar control data can be found on the other Figs). (If the two compartments are both dimly illuminated with red light, mice distribute the time spent in proportion to the size of the compartments.) Preliminary studies testing mice repeatedly in the test box indicated that mice learned to move quickly into the black section where they spent more time: this necessitated the use of mice on one occasion only in the present studies.

In experiments using peripheral vehicle administrations, preliminary studies indicated that the responses of vehicle-injected and non-treated mice were indistinguishable and in the following results only the response of vehicle treated animals is given.

Modification of exploratory behaviour following peripheral administration of buspirone and 5-HT receptor antagonists

The administration of buspirone (0·06 to 2·0 mg kg^{-1} i.p. 30

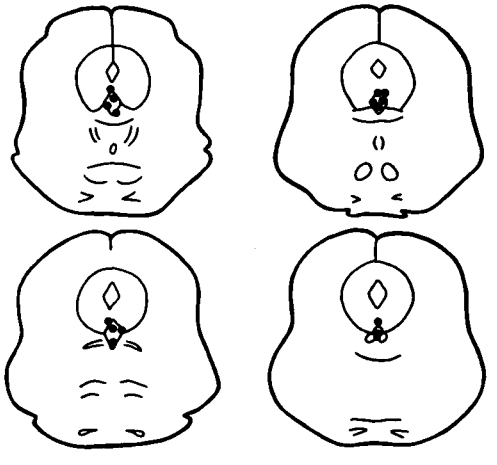

FIG. 1. Diagrammatic representation of the site of injection into the dorsal raphe nucleus of mouse (●). Representative histological data is presented for 15 brains analysed. Injection sites were aimed at the centre of the dorsal raphe nucleus at Ant. 0·5, Vert. 3·1, Lat. 0·0 (the atlas of Slotnick & Leonard (1975) was used as a guide).

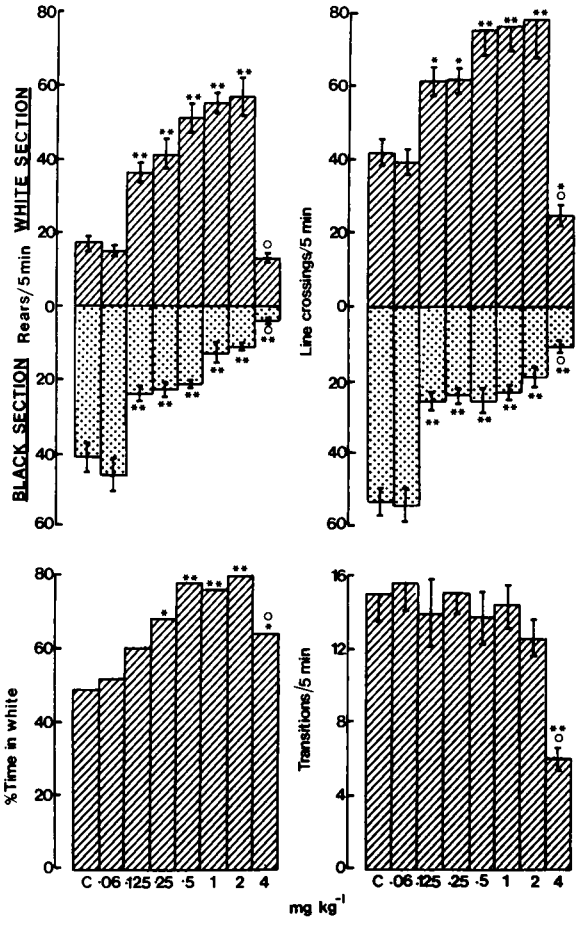

FIG. 2. The effect of buspirone (0·06–4·0 mg kg^{-1} i.p., 30 min pretreatment) on mouse rearing behaviour, line crossings, the % time spent in and transitions between the white and black sections of a box separated into light (white illumination) and dark (red illumination) compartments having an interconnecting 'door'. Measurements were made from remote video recordings taken over a 5 min period. C indicates the response of vehicle-treated control animals. Values represent the mean ± s.e.m.s of 5 determinations; s.e.m.s on the original data for calculation of the % time spent in the white compartment were in the range 7·5–11·6%. Significant increases or decreases in responding compared to control values are indicated $*P < 0·01$ and $**P < 0·001$ (one-way ANOVA followed by Dunnett's t-test) "sedation.

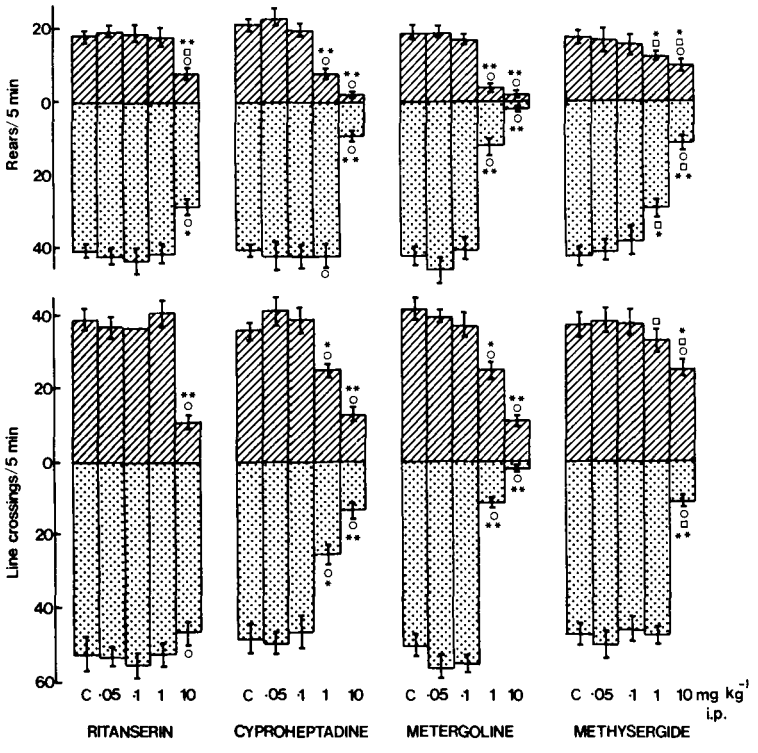

FIG. 3. The effects of ritanserin, cyproheptadine, metergoline and methysergide, administered as 40 min pretreatments, on rearing behaviour and line crossings in the white and black sections of a box separated into light (white illumination) and dark (red illumination) compartments having an interconnecting 'door'. Measurements were made from remote video recordings taken over a 5 min period. C indicates the response of vehicle treated control mice. n = 5. s.e.m.s given. Significant decreases in responding are indicated $*P < 0{\cdot}01$, $**P < 0{\cdot}001$ (one-way ANOVA followed by Dunnett's *t*-test), O sedation, □ ataxia.

min pretreatment) modified exploratory activity by reversing the preference shown in control mice to an increased time spent in the white section of the test system. This was associated with an increase in both rearings and line crossings to 305 and 208%, respectively, of control values, with corresponding decreased responding in the black section. The number of transitions between the two compartments (12 to 16) was unchanged. A dose of 4 mg kg^{-1} buspirone reduced exploratory behaviour in both sections of the test box and animals appeared sedated, reducing transitions between the two compartments (Fig. 2).

The administration of ritanserin, cyproheptadine, metergoline or methysergide in wide dose ranges (0·05–10·0 mg kg^{-1} i.p. 40 min pretreatment) failed to cause specific changes in mouse exploratory activity in the test box. Doses of 0·05 and 0·1 mg kg^{-1} of each compound failed to modify rearings and line crossings in either the white or black sections. However, the use of 1·0 and or 10·0 mg kg^{-1} of all compounds caused reductions in exploratory activity in both the white and black areas, and such reductions were accompanied by sedation and/or ataxia and a decrease in transitions between the two compartments (Fig. 3). It is emphasized that exploratory activity in the white area was never enhanced with the use of any of the above compounds.

Modification of exploratory behaviour following the injection of buspirone and 5-HT into the dorsal raphe nucleus

Behavioural changes were assessed 15 min after intracerebral injection. Buspirone (10 ng) increased the time spent in the white section and enhanced rearings and line crossings to 304 and 183% of control values, respectively, with a decrease in the rearings and line crossings in the black section (by 38 and 39% relative to vehicle-treated controls), notwithstanding that the vehicle itself significantly reduced the measures of exploratory behaviour by 31 and 36% in the black section. The administration of buspirone 20 ng caused similar changes in behaviour whereas a lower dose of 1 ng was ineffective. The transition rate between the two compartments remained unchanged (Fig. 4). The injection of 5-HT (10 ng) into the dorsal raphe nucleus caused a reverse profile of change, that is, reduced rearings and line crossings in the white area with an increased incidence of rearings and line crossings in the black area. The time spent in the black area was increased and the transitions between the two compartments was reduced. The administration of higher doses of 5-HT (25 ng) was associated with inconsistent changes in exploratory behaviour, the variation in response between animals being shown by increased standard errors on the mean values and a return of behaviour towards the control values. In addition, sedation in some animals obscured measures of exploratory behaviour. A lower dose of 5-HT (1 ng) failed to modify mouse exploratory behaviour (Fig. 4).

Modification of exploratory behaviour following the injection of 2-methyl-5-HT into the dorsal raphe nucleus

The characteristic profile of change caused by the injection of 2-methyl-5-HT into the dorsal raphe nucleus was an increased time spent in the black area associated with

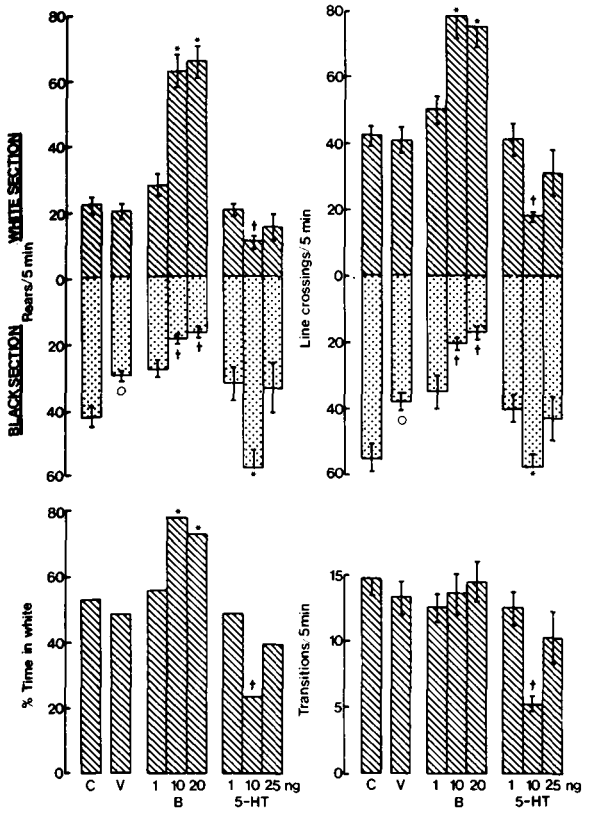

FIG. 4. The effect of 5-hydroxytryptamine (5-HT, 1, 10 and 25 ng) and buspirone (B, 1, 10 and 20 ng) injected into the dorsal raphe nucleus on rearing behaviour and line crossings, the % time spent in and transitions between the white and black sections of a box separated into light (white illumination) and dark (red illumination) compartments having an interconnecting 'door'. Measurements were made from remote video recordings taken over a 5 min period. C indicates the response of non-treated mice and V the response of animals receiving injection of vehicle. n = 5. s.e.m.s given. Significant increases or decreases in responding compared with vehicle-treated controls are indicated as $^{*}P < 0.001$ and $^{+}P < 0.001$, respectively, the significance of the reduction in response of vehicle-treated mice compared with non-treated animals is indicated as $^{\circ}P < 0.05$ (one-way ANOVA followed by Dunnett's *t*-test).

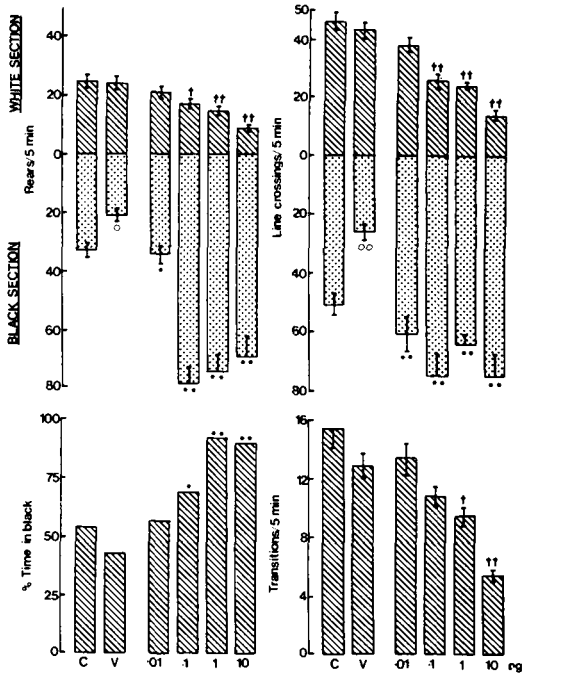

FIG. 5. The effect of 2-methyl-5-hydroxytryptamine (0·01–10 ng) injected into the dorsal raphe nucleus on mouse rearing behaviour, line crossings and the % time spent in and transitions between the white and black sections of a box separated into light (white illumination) and dark (red illumination) compartments having an interconnecting 'door'. Measurements were made from remote video recordings taken over a 5 min period. C indicates the response of non-treated mice, V the response of vehicle treated control mice. Values represent the mean ± s.e.m.s of 5 determinations; s.e.m.s on the original data for calculation of the % time spent in the black section were in the range 9·3–12·1%. Significant increases or decreases in response compared to the vehicle control are indicated $^{*}P < 0.01$, $^{**}P < 0.001$ and $^{+}P < 0.01$ and $^{++}P < 0.001$, respectively; a significant decrease in V compared to C is indicated as $^{\circ}P < 0.05$, $^{\circ\circ}P < 0.01$ (one-way ANOVA followed by Dunnett's *t*-test).

increased rearings and line crossings (to 326 and 191% relative to vehicle controls) and a decreased incidence of rearings and line crossings in the white area (by 28 and 41%). It should be noted that the increased exploratory behaviour in the black area was achieved in the presence of an opposing effect of the vehicle injection itself. The transitions between the two compartments was also reduced although the injection of 2-methyl-5-HT into the dorsal raphe nucleus did not cause any other overt changes in motor behaviour (Fig. 5).

The effect of buspirone and 5-HT receptor antagonists on the changes in exploratory behaviour caused by 2-methyl-5-HT

A dose of buspirone (1·0 mg kg^{-1} i.p.) was selected as causing a reduction of the aversive response in the absence of non-specific motor depression. Doses of ritanserin (1·0 mg kg^{-1}) and methysergide (0·1 mg kg^{-1}) were determined from the above studies as the largest doses that did not cause non-specific motor depression. The potential antagonists were administered i.p. as 40 min pretreatments to the injection of 2-methyl-5-HT (1·0 ng) into the dorsal raphe nucleus and behavioural changes assessed after a further 15 min period. The ability of 2-methyl-5-HT to increase the time spent in the black area, to enhance exploratory behaviour in the black section and reduce rearings and line crossings in the white area, and to decrease transitions between the two compartments was completely antagonised by buspirone. Treatments with ritanserin or methysergide failed to antagonize the effects of 2-methyl-5-HT (Fig. 6).

Discussion

Crawley (1981) has taken an increased exploratory activity in a brightly-lit environment as an index of anxiolytic action when a dark environment is simultaneously available. In the present two-compartment test system, normal mice showed a preference for exploration measured as rearing behaviour, line crossings and time spent in the black section as a consequence of the aversive properties of the brightly lit area. The characteristic action of anxiolytic agents from the benzodiazepine series is to disinhibit the suppressed behaviour causing a redistribution of exploratory activity in the white section (Crawley 1981; Costall et al 1987b). In the present study the peripheral administration of the anxiolytic

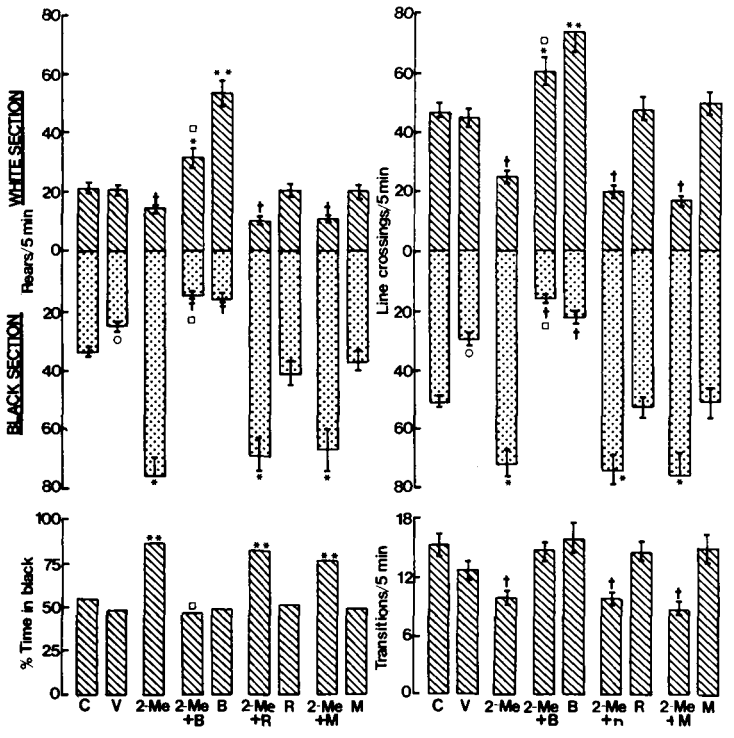

FIG. 6. The effect of the interaction between 2-methyl-5-hydroxytryptamine (2-Me, 1·0 ng) and buspirone (B, 1·0 mg kg^{-1} i.p.), ritanserin (R, 1·0 mg kg^{-1} i.p.) and methysergide (M, 0·1 mg kg^{-1} i.p.) on exploratory behaviour in the mouse. The potential antagonists were administered as 40 min pretreatments to the injection of 2-methyl 5-hydroxytryptamine into the dorsal raphe nucleus. Exploratory behaviour was measured as rearing behaviour, line crossings, % time spent in and transitions between the black and white sections of a box separated into light (white illumination) and dark (red illumination) compartments having an interconnecting 'door'. Measurements were made from remote video recordings taken over a 5 min period. C indicates the response of non-treated animals and V the response of vehicle-treated mice. Values represent the means ± s.e.m.s of 5 determinations; s.e.m.s on the original data for the calculation of the % time spent in the black area were in the range 8·8–13·4%. A significant increase or decrease in response compared to vehicle control values is indicated as $*P<0·01$, $**P<0·001$ and $^{+}P<0·001$ respectively, a significant decrease in V compared with C is indicated $^{\circ}P<0·05$–$0·01$, and a significant difference between the effects of 2-Me and 2-Me + B is indicated as □ $P<0·001$ (one-way ANOVA followed by Dunnett's t-test).

agent buspirone was found to have an identical spectrum of action to that of the benzodiazepines; the response was dose-related and of equal intensity to that reported for diazepam. Such findings support the conclusions from the use of other animal models that buspirone has anxiolytic action (see introduction).

Although it has been reported that the pyrimidinylpiperazine derivatives lack the sedative potential of the benzodiazepines (see review by Traber & Glaser 1987), in the present studies the use of doses of buspirone greater than 2 mg kg^{-1} caused motor impairment to obscure the measurements of changes in exploratory activity. The motor depressant effects of buspirone, possibly related to a neuroleptic effect (Witkin & Barrett 1986), have not apparently been considered in a number of previous negative findings of buspirone action in animal models of anxiety (see review by Chopin & Briley 1987), and may account for the failure to increase punished responding at higher doses.

There is a substantial body of evidence that 5-HT pathways are involved in the control of anxiety, with a reduction in 5-HT function leading to an anxiolytic effect (see reviews by Stein et al 1975; Iversen 1980; Gardner 1985; Chopin & Briley 1987). There is evidence that the anxiolytic effects of buspirone may also relate to an action on the 5-HT systems: the anticonflict effect of buspirone is blocked by lesions of the 5-HT system (Eison et al 1986), buspirone has been shown to displace ligand binding to 5-HT_1 sites (Glaser & Traber 1983; Hall et al 1985) and will mimic the actions of 5-HT to inhibit cell firing in the hippocampal formation and dorsal raphe nucleus after intraperitoneal, intravenous or microiontophoretic application (Van der Maelen & Wilderman 1984; Eison et al 1984). Diazepam has also been shown to enhance the effects of GABA to inhibit cell firing in the dorsal raphe nucleus (Gallagher 1978) and to disinhibit suppressed behaviour in the mouse model following injection into the dorsal raphe nucleus (Costall et al 1987c). Furthermore, the injection of the 5-HT_3 receptor antagonists ICS 205-930 and GR38032F into the dorsal raphe nucleus of the mouse brain will also reduce aversive responding (Costall et al 1987c). The present studies have shown that the injection of buspirone into the dorsal raphe nucleus of the mouse brain has a similar effect indicating the importance of the midbrain cell group to the actions of the benzodiazepines, buspirone and the 5-HT_3 receptor antagonists. It is noteworthy that [^{3}H]ipsaperone, an analogue of buspirone, shows high affinity binding in the dorsal raphe nucleus of the rat brain (Traber & Glaser 1987).

Buspirone can displace [^{3}H]5-HT from limbic tissue by interaction at a 5-HT_{1A} binding site (see Traber & Glaser 1987) and the ability of buspirone to mimic the actions of 5-HT and 5-HT_{1A} receptor agonists to inhibit cell firing in the dorsal raphe nucleus has been taken to support the hypothesis that a component of the anxiolytic action of buspirone may relate to a 5-HT-like action on the 5-HT_{1A} site (see

review by Dourish et al 1986). Within the dorsal raphe nucleus it is considered that the 5-HT_{1A} receptors have a somatodendritic location on 5-HT neurons. An agonist action by buspirone on a presynaptic 5-HT autoreceptor would be expected to decrease 5-HT function throughout the forebrain, and could account for the anxiolytic action of buspirone. If this hypothesis were correct, the injection of 5-HT itself into the dorsal raphe nucleus would be predicted to antagonize an aversive response. However, 5-HT failed to reduce the aversive response of mice to the brightly illuminated arena of the test box and indeed exacerbated the response. The injection of the 5-HT_3 receptor agonist 2-methyl-5-HT (see commentary by Bradley et al 1986; Richardson et al 1985) into the dorsal raphe nucleus also exacerbated the aversive response in the mouse, increasing exploratory rearings, line crossings and time spent in the black area and decreasing their incidence in the white section. In addition, transitions between the two compartments was decreased. A similar profile of action is obtained in the mouse model following the peripheral injection of the anxiogenic β-carboline compound, FG 7142 (Costall et al, unpublished data) and an anxiogenic profile is observed in the rat social interaction test following the injection of methyl-β-carboline-3-carboxylate into the dorsal raphe nucleus (Hindley et al 1985).

Whilst the present findings support a role for 5-HT in the dorsal raphe nucleus in aversive responding, unlike results from electrophysiological experiments, buspirone does not appear to mimic the actions of 5-HT. This may reflect a number of factors. Firstly, buspirone is not a pure 5-HT_{1A} agonist, it also has 5-HT_{1A} antagonist potential (see reviews by Dourish et al 1986; Fozard 1987) and its effects may be dependent on basal 5-HT tone. If it is accepted that 5-HT may stimulate a 5-HT_{1A} receptor in the DRN to enhance aversive responding then the anxiolytic action of buspirone may reflect a 5-HT_{1A} antagonist effect. This hypothesis could be tested using a selective 5-HT_{1A} antagonist, but no such compounds are presently available. Nevertheless, it should be noted that 5-methoxy-*N,N*-dimethyltryptamine which has 5-HT_{1A} receptor agonist activity shows an anxiogenic profile in the elevated plus-maze test (Critchley & Handley 1986). It remains interesting to speculate that in animal models of anxiety the markedly inconsistent actions of buspirone and other agents interacting at the 5-HT_{1A} receptor may reflect an agonist/partial agonist/antagonist effect and the degree of 5-HT tone (see Dourish et al 1986). The failure of agents such as methysergide, cyproheptadine and metergoline to modify anxiety in the mouse model may reflect their non-selective actions on 5-HT_1/5-HT_2 receptors. The failure of ritanserin to modify anxiety, at least in the mouse black and white test box or conflict test (Colpaert et al 1985; Dourish et al 1986), indicates an unimportant role for 5-HT at 5-HT_2 receptors in the dorsal raphe nucleus.

A further potential site of interaction of buspirone with 5-HT mechanisms is via the 5-HT_3 receptor. 5-HT_3 receptor antagonists have potent anxiolytic profiles of action in the mouse model (Costall et al 1987a; Tyers et al 1987) in contrast with the anxiogenic profile of action following the injection of 2-methyl-5-HT into the dorsal raphe nucleus. The peripheral administration of buspirone was shown to prevent the anxiogenesis induced by 2-methyl-5-HT, but this was shown by a dose of buspirone having an anxiolytic action in its own right, lower doses are ineffective (Costall et al, unpublished data). It is unlikely that buspirone can directly antagonize the effects of 2-methyl-5-HT since buspirone has no 5-HT_3 receptor antagonist action on the rabbit vagus nerve or in 5-HT_3 radioligand binding assays (Costall et al unpublished data). This may indicate that the antagonism exerted by buspirone is indirect and possibly indicative of a functional interaction between the 5-HT_{1A} and 5-HT_3 sites. Also, it should be noted that unlike the effects observed with 2-methyl-5-HT, the anxiogenic action of 5-HT became less at a higher dose. This may indicate a further site of action of 5-HT to oppose anxiogenesis and a balance between a facilitatory and inhibitory 5-HT control of anxiety has been hypothesized previously by Gardner (1986). It is clear that to confirm or disprove such a hypothesis will require the use of highly selective agonists and antagonists at the different 5-HT receptor subtypes in future work.

In summary, the studies provide evidence that buspirone administered peripherally or into the dorsal raphe nucleus reduces an aversive response in a mouse model. If such changes can be related to changes in anxiety, then the dorsal raphe nucleus may be an important locus of anxiolytic action where the precise interaction between buspirone and the 5-HT systems remains to be determined.

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