Pharmacology Biochemistry and Behavior, Vol. 43, pp. 167–171, 1992
Printed in the U.S.A.

0091-3057/92 $5.00 + .00

Buspirone Produces a Dose-Related Impairment in Spatial Navigation

N. McNAUGHTON*[1] AND R. G. M. MORRIS†

*Department of Psychology, University of Otago, POB 56, Dunedin, New Zealand
†Department of Pharmacology, University of Edinburgh, Edinburgh, Scotland

Received 3 June 1991

McNAUGHTON, N. AND R. G. M. MORRIS. *Buspirone produces a dose-related impairment in spatial navigation.* PHARMACOL BIOCHEM BEHAV 43(1) 167–171, 1992.—Classical anxiolytic drugs and hippocampal lesions have common behavioural effects that include loss of place navigation in the water maze. The novel anxiolytic drug buspirone, unlike classical anxiolytic drugs, does not interact with GABA and is not muscle relaxant, sedative, hypnotic, anticonvulsant, or addictive. Buspirone affects hippocampal electrophysiology in a similar fashion to classical anxiolytics and so we predicted it would have similar effects on spatial navigation. Rats injected with buspirone (0.1–10.0 mg/kg, IP) showed a loss of acquisition of spatial navigation in the water maze that has a similar dose dependence to that reported for the effects of buspirone on the hippocampus. This finding demonstrates that the effects of anxiolytics on spatial navigation are not due to their side effects and supports the view that changes in hippocampal function may underlie some components of clinical anxiolytic action.

Buspirone Anxiety Spatial navigation Hippocampus Rat

TWO theories of hippocampal function have been elaborated in detail. O'Keefe and Nadel (18) proposed that the hippocampus contains a map crucial for spatial navigation in rats and crucial for more general cognitive mapping in humans. Gray (7) proposed that the hippocampus is a comparator crucial to the correct functioning of a behavioural inhibition system. The major difference between Gray, on the one hand, and O'Keefe and Nadel (or, indeed, most other hippocampal theorists), on the other, is his emphasis on the effects of anxiolytic drugs.

There are marked similarities between the behavioural effects of anxiolytic drugs and the effects of hippocampal lesions (7). This is not entirely surprising since anxiolytic drugs are known to affect the control of hippocampal rhythmical slow activity (RSA) in two separate ways: They increase the threshold for elicitation of RSA by septal stimulation (8,11) and, through neurophysiologically and pharmacologically different mechanisms, impair reticular elicitation of RSA (1, 14,15).

In this context, it is particularly interesting that a relatively low dose of the anxiolytic benzodiazepine chlordiazepoxide in the rat impaired acquisition of spatial memory in the open-field water maze (13), a particularly sensitive test of hippocampal dysfunction (17). This effect has also been found with a second benzodiazepine, diazepam, and is not obtained if the drug is administered after acquisition of the task is complete (Skelton and McNamara, personal communication).

All the above data are consistent with the view that anxiolytics have important behavioural effects through a direct or indirect action on the hippocampus. However, it is also possible that the observed behavioural and hippocampal effects of the drugs are unrelated.

All classical anxiolytics (benzodiazepines, barbiturates, meprobamate, ethanol) act, by differing routes, to increase GABA transmission (25). They also all share, in addition to anxiolytic action, muscle relaxant, anticonvulsant, hypnotic, and addictive properties. The hippocampal effects of the drugs could well, therefore, be a result of their anticonvulsant action, for example, rather than their anxiolytic action.

The novel anxiolytic buspirone provides a means of testing this possibility. Buspirone is as potent clinically as the benzodiazepine diazepam. However, it does not interact with GABA and its side effects do not overlap with those of the classical anxiolytics (4,27,28). Buspirone affects hippocampal electrophysiology in a similar (but not absolutely identical) manner to classical anxiolytics (10). However, in conventional animal models of anxiolytic action buspirone has atypical, weak, or variable effects (3,16,20–22,24).

In the present experiments, therefore, we investigated the effects of buspirone in the water maze as a test of its functional effects on the hippocampus. A dose of 2 mg/kg buspirone has already been reported to impair acquisition of this task (23). Buspirone shows threshold effects on the frequency of hippocampal RSA in the region of 0.1 mg/kg and very

[1] To whom requests for reprints should be addressed.

large reductions in frequency at doses of 10 mg/kg and above [(10); unpublished data]. A dose-response curve was therefore obtained in the range 0.1–10.0 mg/kg to allow comparison with the electrophysiological effects of the drug.

METHOD

Subjects

Subjects were 40 naive, male Lister-Hooded rats weighing between 300–460 g. They were caged singly at a temperature of 22 ± 1°C and with food and water freely available.

Apparatus

The pool was 2.00 m diameter, 0.60 m high, and filled to a depth of 0.4 m with water at 26°C to which was added the equivalent of approximately 5 pints of milk in the form of reconstituted milk powder. The target platform was 0.10 m in diameter and located 0.01–0.015 m beneath the surface of the water. Starting points for animals were marked on the outside of the pool as N, S, E, and W, but their location did not correspond to geographical direction. The target was located in the centre of the NW or SE quadrant at a point 0.33 m from the side of the pool. Above the pool was mounted a videocamera that, together with circular marking screens and suitably located lighting, allowed a view of the surface of the pool with even illumination. The camera was connected to an HVS image analyser that provided a readout of the X–Y coordinates of rats' location by tracking their heads. These coordinates were captured by an Acorn Archimedes computer using WATERMAZE software (available via Paul Fray Ltd., Cambridge, UK).

Group Assignment and Drugs

Twenty rats were assigned to each of five doses of buspirone hydrochloride. They were run in the same order each day with the same drug throughout the experiment. The order of doses was [0.0, 0.1, 0.3, 1.1, 3.3,], [3.3, 1.1, 0.3, 0.1, 0.0,], [3.3, 1.1, 0.3, 0.1, 0.0,], and [0.0, 0.1, 0.3, 1.1, 3.3]. There were, thus, four rats in each dose condition. After the first 20 rats had completed testing, the second 20 were assigned to dose in a similar manner except doses ran from 0.3–10.0 mg/kg rather than 0.1–3.3 mg/kg and the counterbalancing sequence was reversed: [10.0, 3.3, 1.1, 0.3, 0.0,], [0.0, 0.3, 1.1, 3.3, 10.0,], [0.0, 0.3, 1.1, 3.3, 10.0,], and [10.0, 3.3, 1.1, 0.3, 0.0]. In both sets of 20 rats, the first 10 swam to a platform at NW and the second 10 to a platform at SE. All doses were administered IP at 1 ml/kg in saline 20–30 min before testing (depending upon the performance of previous rats).

Training

For each trial, the rat was placed in the water at one of the four starting points and recording of the trial was initiated as it was released. The rat was allowed to swim freely until either it had climbed onto the platform (at which point recording was terminated) or 120 s had elapsed. When the 120 s criterion had been exceeded, the rat was placed gently on the platform (first two trials) or (later trials) the experimenter indicated the position of the platform by placing his hand over it. The rat remained on the platform for 15 s and was then placed in the pool at the next starting position except after the last trial of each day, when it was removed, immediately dried with a towel, and placed under heat lamps until dry.

Four acquisition trials were given per day for 3 days. The starting positions on successive trials were the same for all rats and were in the order NEWS, WSNE, and SWEN for the first 20 rats and NSEW, SNWE, and EWNS for the second 20.

Transfer Test

On the day following acquisition, a single transfer test was given that was identical to ordinary training trials except the platform was not present in the pool. Rats were allowed to swim freely for 60 s and then were removed from the pool. For the transfer test, all rats started from E.

Data Collection and Analysis

In all trials, we recorded latency to escape and path length. Swimming speed was calculated as path length divided by latency. For the transfer test, we also recorded the amount of time and distance the animal spent in each quadrant of the swimming pool; the time spent within 0.05 m of the sidewalls; and the number of times the animal passed through a nominal annulus 0.11 m in diameter at the location in each quadrant at which the platform could have been placed. An angular or logarithmic transformation was applied where necessary to normalise the data (29) and the data were then submitted to analysis of variance (ANOVA). For the acquisition data, orthogonal polynomial components of effects involving days and trials were extracted (26). The linear component extracted by this method is identical to the slope of the least-squares regression fitted to the relevant means and higher-order components represent symmetrical curves with increasing numbers of inflexions. The data from the two experiments were analysed together so that all doses were represented by two separate groups ($n = 4$) except for the single 0.1- and 10.0-mg/kg groups.

RESULTS

Acquisition

With the exception of two rats in the 10-mg/kg dose group, all rats appeared to swim efficiently. The two exceptional rats showed an abnormal, rolling swimming pattern and occasionally floated without swimming at the start of a trial. One of these tended not to mount the platform when it was reached, but instead placed only its forepaws on the platform. Buspirone reduced overall swimming speeds in a dose-related manner [linear $F(1, 30) = 10.1$, $p < 0.005$] with some nonlinear interactions [e.g., dose × days, cubic × linear $F(1, 60) = 5.7$, $p < 0.025$]. By the end of acquisition, mean speeds in the two control groups were 0.23 and 0.24 m/s. Rats receiving 0.1–1.0 mg/kg buspirone swam at similar speeds to controls, but one of the two 3.3-mg/kg groups swam slightly slower (0.20 and 0.23 m/s) and the 10-mg/kg group swam much slower (0.15 m/s). Because of the changes in speed, latency to mount the platform will not be discussed as a measure of navigation.

Buspirone impaired acquisition of the water maze task, demonstrated by increases in path length, in a dose-related manner. Drugged rats found the platform as easily as control rats on the first trials of training but took longer paths later in training. The effects were dose related [Fig. 1; dose, linear $F(1, 30) = 22.4$, $p < 0.0005$; dose × trials, linear × linear $F(1, 270) = 6.3$, $p < 0.025$]. However, the 1.1- and 3.3-mg/kg doses showed relatively faster acquisition than other doses across days as opposed to trials [dose × days, cubic × linear $F(1, 60) = 8.4$, $p < 0.005$].

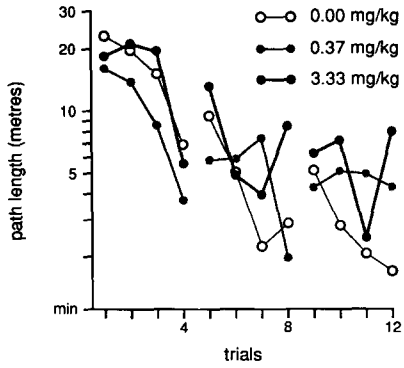

FIG. 1. Effects of buspirone on acquisition of spatial navigation in the open-field water maze. Four trials were given per day for 3 days. Path length is plotted as an indication of accuracy of spatial navigation and the nonlinear axis is the result of the logarithmic transformation [$X' = \log_{10}(X)$] required for ANOVA of the data. Three representative examples (0.0, 0.3, and 3.3 mg/kg) are shown from the first of the two sets of rats tested with doses in the range 0.1–10.0 mg/kg. Each point is the mean over only four rats for a single trial and so there is a large variability between trials. A dose-related impairment of acquisition is apparent across days and was replicated across doses and experiments.

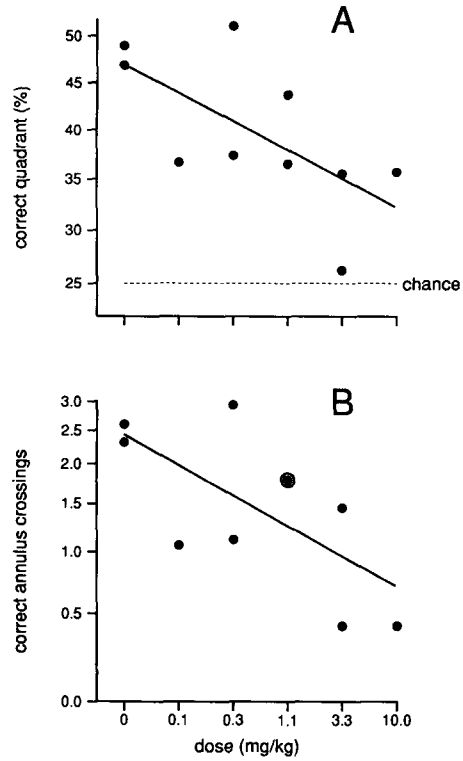

FIG. 2. Effects of buspirone in a transfer test carried out after acquisition of spatial navigation in the open-field water maze. This test was carried out to analyse the basis of the differences between the groups that were evident at the termination of acquisition (no groups had reached asymptote at this point). Conditions were identical to acquisition except there was no platform in the pool. The test lasted 60 s. The data plotted are means for four animals. Each dose is replicated except 0.1 mg/kg (first batch of rats only) and 10.0 mg/kg (second batch of rats only). The straight lines reflect the significant linear regressions on dose detected by ANOVA. (A) Percentage of time spent in the previously correct quadrant of the pool. The nonlinear axis is the result of angular transformation. (B) Number of times the animal passed through a nominal annulus defining the previous location of the platform. The nonlinear axis is the result of the logarithmic transformation [$X' = \log 10 (X + 1)$] required for ANOVA of the data.

Transfer Test

There may have been a slight tendency for buspirone rats to swim close to the side of the maze during the transfer test, but this did not achieve conventional levels of significance [dose linear $F(1, 30) = 3.97$, $0.05 < p < 0.10$]. Percentage of time spent in the previously correct quadrant was reduced linearly with increasing dose of buspirone [Fig. 2A; $F(1, 30) = 4.6$, $p < 0.05$]. Number of correct annulus crossings, probably the best measure of accuracy of spatial navigation as opposed to nonspatial strategies, was also clearly reduced linearly with increasing dose of buspirone [Fig. 2B; linear $F(1, 30) = 9.1$, $p < 0.01$]. As with our previous experiment with chlordiazepoxide (13), number of incorrect annuli crossed was not affected (all $F < 1.0$).

DISCUSSION

The critical finding of the present experiment is that correct annulus crossings in the transfer test were reduced linearly with respect to dose of buspirone. This demonstrates a similar loss of spatial navigation to that previously reported with a 5-mg/kg dose of chlordiazepoxide (13) and with 2 mg/kg buspirone (23). This effect of anxiolytics is, therefore, general to very different classes of drugs and to varying doses.

This common effect of buspirone and classical anxiolytics may well relate to their clinical efficacy. None of the reported side effects of buspirone are shared by chlordiazepoxide and the effective doses of both drugs in the water maze are at the low end of their dose-response curves in most other behavioural tests.

It is interesting to note that higher doses of buspirone decreased swimming speed. By contrast, chlordiazepoxide increased swimming speed in our previous experiments (13). It is possible, therefore, to have opposite effects of anxiolytic drugs on swimming speed while having similar effects on acquisition as assessed by path length and particularly transfer test scores.

The results of the present experiment are largely similar to those reported by Rowan et al. (23) Extrapolation from our data shows that a 2-mg/kg dose of buspirone would halve correct annulus crossings and produce a reduction of 10% in correct quadrant time in the transfer test—very similar to Rowan et al.'s results. There is an apparent discrepancy in acquisition in that many of our drug groups were similar to control at the beginning but not the end of each block of four daily trials, whereas Rowan et al. show the reverse within-day trend. However, some of our drug groups showed the same trend as Rowan et al. This was not systematically related to dose. None of our drug groups showed the large deficit in trial 1 obtained by Rowan et al. This could, in part, be due to our use of a 120-s maximum trial length as opposed to their 180-s maximum. However, many of our drug groups (including the highest dose groups) were no different than controls. The most likely causes of this trial 1 discrepancy are: a) pool temperature (26 v. 23°C); b) strain of rat (Lister hooded v. Wistar albino); and c) weight of rat (300–460 g v. 200 g).

Buspirone is known to release corticosterone at doses above 1 mg/kg (2) and this may have combined with stress induced by the colder water (and perhaps type of rat) used by Rowan et al. to depress swimming. It is perhaps consistent with this hypothesis that our two control groups swam slower than Rowan et al.'s on the first trial (97 and 99 v. 65–70 s.). Whatever the causes of these acquisition differences, they clearly have not affected the crucial transfer test results, which show extremely close agreement between the two studies.

The linearity of buspirone's dose–response curve with this test of spatial navigation is relatively unusual. In a variety of animal models of anxiety, buspirone has no effect or, where it does act like an anxiolytic, produces weak effects with a dose–response curve that reverses in the region of 1.0 mg/kg (3,16,20–22,24). However, buspirone does show a linear dose–response curve with its reduction of rearing in a low-stress open field (19) and with its reduction in the frequency of hippocampal RSA (10). Given the limits of accuracy both within and between experiments, it appears that spatial navigation, rearing, and RSA frequency reduction have quantitatively similar dose–response curves and that for all three tests the dose of buspirone equivalent to 5 mg/kg chlordiazepoxide is the same: in the range 1–3 mg/kg.

As with our previous results with chlordiazepoxide, buspirone did not produce the massive impairment in acquisition of spatial navigation seen with hippocampal lesions. This suggests that while anxiolytic drugs abolish acquisition of spatial navigation proper they leave intact other strategies that allow a partial, less efficient, solution to the problem (13). It is important to note that both with benzodiazepines and buspirone the drugs have minimal effects if given after acquisition is complete [Skelton and McNamara, personal communication; (23)]—this indicates an action on some aspect of learning rather than on spatial navigation itself.

While it could be argued that the water maze involves negative reinforcement, it is unlikely that the anxiolytic drugs affect the task for this reason. Performance of the task involves active as opposed to passive avoidance and active avoidance tasks, by contrast to passive avoidance tasks, are spared by anxiolytic drugs (6). The most likely basis for the deficit, therefore, is some failure of complex stimulus processing.

Gray (5) first remarked on the similar behavioural effects of the anxiolytic barbiturate sodium amylobarbitone and septohippocampal lesions. Since then, this similarity has been extended to all classes of classical anxiolytic drugs (6) and to a very extensive range of behaviours (7). There is good reason to attribute this common behavioural profile to at least two distinct actions the anxiolytic drugs have on septohippocampal electrophysiology (9,12). The fact that buspirone shares both these actions on hippocampal electrophysiology (10) and also affects spatial navigation in the water maze is striking given its general lack of similarity to classical anxiolytics on most electrophysiological and neurochemical measures and its limited similarity on other behavioural tests.

The present results suggest, therefore, that "spatial" and "anxiety" views of the hippocampus may derive from test-specific aspects of some more general cognitive operation. This operation could involve some class of cognitive operation. This operation could involve some class of relation between numbers of complex stimuli basic to the assessment of both spatial relationships and, for example, risk. On this view, anxiolytics could act on the hippocampus to affect cognitive, but only indirectly spatial, processing in the water maze and cognitive, but only indirectly emotional, processing in anxiety.

ACKNOWLEDGEMENTS

This work was supported by a grant to R.G.M.M. from the British Medical Research Council. Buspirone was kindly supplied by Bristol-Myers.

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