Pharmacology Biochemistry & Behavior, Vol. 28, pp. 15–20. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Barrel Rotation in Rats Induced by Intracerebroventricular Bradykinin Antagonists

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Received 9 March 1987

PERRY, D. C. *Barrel rotation in rats induced by intracerebroventricular bradykinin antagonists.* PHARMACOL BIOCHEM BEHAV **28**(1) 15–20, 1987.—Intracerebroventricular (ICV) administration of bradykinin (BK) analogs containing the substitution DPhe^7 produced extreme postural distortions within 2–4 min after injection, eventually causing rats to spin repeatedly around their longitudinal axis. This behavior, called barrel rotation, has been previously reported following ICV administration of several other neuropeptides. Episodes lasted 5–20 min; two deaths occurred at high doses, but no other long-term effects were observed. The quantal ED_{50} of the prototype compound B4162 (DArg^0, Thi^{5,8} DPhe^{7}BK), was 14.9 nmole; all seven other DPhe^7 analogs tested elicited a positive response at 20 nmole. Among analogs not containing DPhe^7, only BK elicited any activity (20% response rate), and only at 100 nmoles. Structure-activity considerations indicate that this behavior is not mediated by classical kinin receptors. The response rate to 20 nmole B4162 (81%) did not significantly change after pretreatment with ICV BK (100 nmoles), or IP atropine, haloperidol or phenytoin; whereas pretreatment with ICV captopril and muscimol and IP naloxone, diazepam and phenobarbital all significantly inhibited the response. A GABAergic mechanism may be involved in this peptide behavior.

Bradykinin Kinin antagonists Barrel rotation Intracerebroventricular injection D-Amino acids Anticonvulsants Gamma aminobutyric acid (GABA)

BRADYKININ (BK) is present in mammalian brain [9,22], and causes various pharmacological responses following intracerebroventricular (ICV) administration, including an increase in blood pressure and heart rate, an increase in pain threshold, antidiuresis, EEG changes, and a behavioral syndrome of rapid and short-lived excitation followed by prolonged sedation and sometimes catalepsy [7,21]. Stewart and Vavrek [29] recently described the synthesis of specific BK antagonists, which have been found to act via competitive BK receptor blockade [19,29]. In order to better understand the physiological role of BK in the central nervous system (CNS), I undertook to study the effects of ICV BK antagonists in rats.

In initial experiments, ICV administration of BK antagonists precipitated a unique behavior known as barrel rotation. Barrel rotation (BR) is a violent motor disturbance first reported to follow ICV injections of somatostatin to rats [8]. It consists of multiple, rapid rotations around the animal's longitudinal axis. It was subsequently demonstrated to occur following ICV administration of a number of neuropeptides, including vasopressin [1, 2, 11, 14, 16, 17, 30, 31], substance P [26], cholecystokinin (27–33) [18] and dynorphin [12, 13, 23], as well as the antimuscarinic agent chlorpromazine methiodide [3, 5, 6, 27].

Further studies were undertaken in order to characterize the BR response to BK antagonists. The structure-activity relation of BR was found not to be the same as for classical kinin responses. Furthermore, inhibitor studies suggested a possible involvement with gamma aminobutyric acid (GABA) receptors in the brain.

METHOD

Male Sprague-Dawley rats (250–350 g) were implanted with intraventricular cannulae under pentobarbital anesthesia (45 mg/kg IP). Animals were mounted in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA), with the incisor bar down 10.0 mm; a burr hole was drilled at a point 1.5 mm left and 1.0 mm posterior to the bregma, and a 22 ga stainless steel guide cannula (Plastic Products, Roanoke, VA) was implanted into the lateral ventricle to a depth of 4.6 mm. The guide was secured to the skull with three screws and cranioplastic cement (Plastic Products), and closed by screwing on a dummy cannula. Animals were injected SC with 0.2 ml Flocillin, a broad-spectrum antibiotic (Bristol Laboratories, Syracuse, NY) and allowed to recover 3–5 days. Injections were done with a 10 μl Hamilton syringe connected by PE-20 tubing to a 28 ga internal cannula (Plastic Products) which was inserted into the guide cannula to a final depth of 5.6 mm.

Drugs were administered in 5 μl of 10 mM phosphate-buffered saline, pH 7.4 (PBS); doses were calculated as nmoles free base. Administration was over a 30 sec period,

TABLE 1
STRUCTURES OF BRADYKININ ANALOGS

Name		1	2	3	4	5	6	7	8	9
Bradykinin (BK)		Arg	Pro	Pro	Gly	Phe	Ser	Pro	Phe	Arg
Kallidin (LysBK)	*Lys-*	Arg	Pro	Pro	Gly	Phe	Ser	Pro	Phe	Arg
MetLysBK	*Met-Lys-*	Arg	Pro	Pro	Gly	Phe	Ser	Pro	Phe	Arg
IleSerBK (T-kinin)	*Ile- Ser-*	Arg	Pro	Pro	Gly	Phe-	Ser-	Pro	Phe	Arg
DesArg^9-BK		Arg-	Pro	Pro	Gly	Phe	Ser	Pro	Phe	
B1324		Arg-	Pro	Pro	Gly	*Thi*	Ser	Pro	*Thi*	Arg
B3600		Arg	Pro	Pro	Gly	Phe	Ser	*DPhe*	Phe	Arg
B3814	*Lys-Lys-*	Arg	*Hyp*	Pro	Gly	*Thi*	Ser	*DPhe*	*Thi*	Arg
B3816	*DArg-*	Arg	*Hyp*	Pro	Gly	*Thi*	Ser-	*DPhe*	*Thi*	Arg
B3820		Arg	Pro	*Hyp*	Gly	*Thi*	Ser	*DPhe*	*Thi*	Arg
B4162	*DArg*	Arg	Pro	*Hyp*	Gly	*Thi*	Ser	*DPhe*	*Thi*	Arg
B3832	*DArg*	Arg	*Hyp*	*Hyp*	Gly	*Thi*	Ser	*DPhe*	*Thi*	Arg
B3926		Arg	Pro	Pro	Gly	*Thi*	Ser	*DPhe*	*Thi*	Arg
B4046	*Eac - Eac*	Arg	Pro	Pro	Gly	*Thi*	Ser	*DPhe*	*Thi*	Arg

Thi=β-(2-thienyl)-alanine; Hyp=hydroxyproline; Eac=epsilon-amino caproic acid.

and the internal cannula was left in place for another 30 sec before removal and reclosure. Cannula placement was assessed by injection of 3 μl of Brilliant blue dye; animals were then sacrificed and brains removed and examined for presence of dye throughout the ventricular system. Those lacking ventricular dye were excluded. Animals were tested from 1–5 times before sacrifice, with at least 24 hours between tests.

For experiments involving inhibition by BK or captopril, the inhibitor (dissolved in 4 μl PBS) was pulled into the syringe, followed by 1 μl air, and 5 μl test drug; inhibitor was administered from 0 to 30 sec, while test drug was administered from 60 to 90 sec. Muscimol was administered ICV 10 min prior to test drug, while other inhibitors were administered IP 30 min prior to test drug (45 min for haloperidol). Animals were placed in a 24×48×18 cm open metal cage lined with cardboard; the direction and number of longitudinal rotations were counted and the time after injection of initial onset noted. A positive response was considered to be one or more rotations within 60 min. Statistical comparison of different treatments was done using Fisher's Exact Test.

Bradykinin, LysBK, MetLysBK, IleSerBK, [DPro^2, DPhe^7, DTrp^9] substance P and DesArg^{9}BK were obtained from Bachem (Torrance, CA); all other kinin peptides were synthesized by and were gifts from Drs. Raymond Vavrek and John M. Stewart. Muscimol was a gift from Dr. Judy Walters; phenobarbital a gift from Dr. Fred P. Abramson; and naloxone and haloperidol a gift from Dr. Solomon H. Snyder. Captopril was obtained from E. R. Squibb (Princeton, NJ), diazepam from Roche Pharmaceutical (Nutley, NJ) atropine sulfate and D-phenylalanine HCl from Sigma Chemical (St. Louis, MO), and phenytoin sodium from Elkins-Sinn, Inc. (Cherry Hill, NJ).

RESULTS

The BK antagonist analog B4162 (see Table 1 for structure) was chosen as a prototype compound; the reference dose was 20 nmole. Barrel rotation induced by ICV BK antagonists usually began within 2–4 min after injection (mean 194 sec ± 27 S.E.). Immediately prior to the initial rotation, animals exhibited a distinctive behavioral syndrome: at 1^1/$_2$–2 min, vigorous grooming and occasional active sniffing was observed, sometimes alternating with periods of immobility and staring; this was followed by various abnormal motor activities, including backwards walking, ataxia, head waving, leading to a spastic abduction of the forelimb and hindlimb on one side. Most (but not all) of the animals that exhibited these "prerotation" symptoms proceeded rapidly to actual rotations. Rotational behavior was episodic; bursts of many rapid rotations would alternate with periods of no rotation, when animals were immobile and staring, appearing cataleptic. During these periods, animals could often be stimulated to resume rotations by light handling. Bulging eyes and horizontal nystagmus were often noted during these interludes, as well as during rational behavior. Few episodes lasted longer than 15 min; afterwards, animals appeared sedated but were otherwise normally responsive. Two animals receiving high doses died within 10 min after initiating rotations, probably from lung edema; no other obvious ill-effects were detected in any other animals, which appeared completely recovered within 1–2 hr.

The total number of turns in one episode ranged from 1 to 186; in one group of 18 animals receiving 20 nmoles B4162, the mean number of rotations was 51 (±8 S.E.). The number of rotations in this group of animals appeared to be dose-dependent: rats that responded to 5 nmole B4162 rotated an average of 19 times; to 15 nmoles B4162 24 times; and to 30 nmole B4162 73 times per episode. In contrast, the latency (time to onset of first rotation) showed no dose relationship. The direction of rotation did not show a consistent pattern. Although all 30 rats were cannulated on the same (left) side, 14 rotated only to the left, 10 to the right, and 6 alternated the direction of rotation during an episode. Of eleven rats monitored that exhibited more than one episode of rotation on different days, 6 rats rotated consistently in the same direction, while 5 rotated in a different direction on different days.

As this behavior has not been previously reported for ICV

TABLE 2
BARREL ROTATION INDUCED BY BRADYKININ ANALOGS

Peptide	Dose (nmoles)	BR*
BK	25	0/10
BK	50	0/11
BK	100	2/10
Lys BK	50	0/4
MetLys BK	50	0/1
T-Kinin	35	0/1
DesArg^{9}BK	60	0/1
B1324	60	0/5
B3600	10	0/2
B3600	20	9/17
B3600	50	1/1†
B3814	20	1/1
B3816	20	2/4
B3820	20	5/5
B3832	20	2/2
B3926	20	4/8
B4046	20	1/3
B4162	5	2/10
B4162	10	2/10
B4162	15	3/6
B4162	20	21/26
B4162	30	6/7
B4162	100	1/1†

*Number animals rotating/number tested.
†Animal died.

BK or BK analogs, a variety of analogs were tested for their ability to elicit BR. The structures of these analogs are shown in Table 1. BK, kallidin, MetLysBK, IleSerBK (= T-kinin) and B1324 all exhibit standard kinin agonist activity in all assay systems [24]. DesArg^{9}BK shows neither agonist nor antagonist activity in classical kinin systems, but is active at the "B-1" kinin receptor [24]. The remaining BK analogs, which all share the DPhe^7 substitution, exhibit either partial or pure antagonist activity in both *in vitro* and *in vivo* assay systems [19,29]. Of the eight analogs containing DPhe^7, all induced barrel rotation at a dose of 20 nmole (Table 2), including the simplest analog, B3600 (= DPhe^{7}BK). Of those without the DPhe^7 substitution, i.e., agonist analogs, no effects were seen in doses up to 60 nmoles (Table 2). However, BK itself did induce BR in 2 of 10 animals at a dose of 100 nmoles. These two animals began rotation to the right, then later switched to the left. No other overt behavioral effects, including the above-mentioned pre-rotation symptoms, were noted in animals receiving BK agonists at doses of 60 nmoles and below.

The quantal dose-response curve for the prototype B4162 is shown in Fig. 1; probit analysis of the response for 10–30 nmoles yielded an ED_{50} value of 14.9 nmole. Complete dose-response studies were not done with other antagonist compounds. Nevertheless, these compounds showed a 33–100% response rate at 20 nmoles, indicating a roughly similar potency for all of them (B3820 may possibly be more potent and B3600 and B3926 appear to be less potent). Dose-response data for BK, the only active analog without DPhe^7, indicate an ED_{50} significantly greater than 100 nmoles.

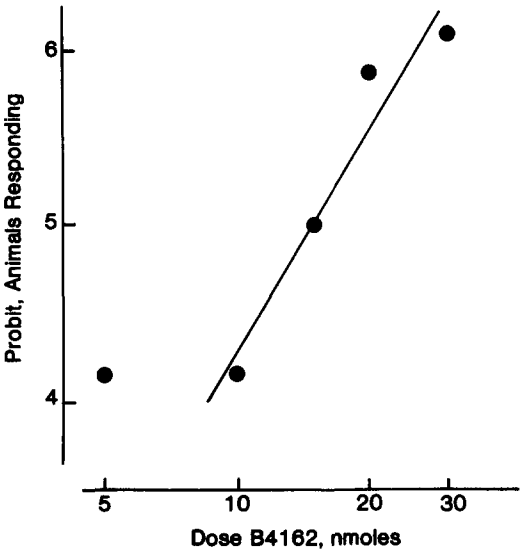

FIG. 1. Probit analysis of the quantal dose-response relationship for barrel rotation induced by ICV B4162. Least-squares regression line shown for doses greater than 10 nmoles.

The ability of d-phenylalanine to elicit BR was tested with five animals. Each received one dose of d-phenylalanine HCl, either 20, 40, 60, 80 or 100 nmoles; no evidence of BR or any other unusual behavior was seen in 30 min of observation. [DPro^2, DPhe^7, DTrp^9]substance P (100 nmoles ICV) induced BR in 1 of 2 rats.

The pharmacology of the BR response to BK antagonists was explored by comparing the ability of various compounds to attenuate the response rate to a standard dose of 20 nmole B4162. If the BR response was due to competitive antagonism at receptors for endogenous BK in the CNS, it might be prevented by pretreating with a large amount of the agonist. Neither 50 or 100 nmole BK given ICV 1 min prior to the challenge dose altered the response. Pretreatment with captopril, an inhibitor of angiotensin converting enzyme (ACE), has been shown to enhance and prolong the effects of ICV BK in rats [21]. Similar enhancement of the BR response to B4162 might also be expected if ACE similarly degrades DPhe^7-containing BK analogs. Moderate captopril doses (10 nmole) showed no effect (not shown). Surprisingly, however, a higher dose (50 nmole) actually produced a small but statistically significant decrease in the response rate to the test dose of B4162 (Table 3). Captopril alone (50 nmole) had no effect in four animals.

Among those animals pretreated with 50 nmole captopril that still responded to B4162, the intensity of response appeared attenuated. In an attempt to quantitate this observation, latency times (time from injection of B4162 to first BR) and total number of rotations were compared in 18 control animals (B4162 only) and seven captopril-treated animals. Captopril pretreatment increased latency 23%, and decreased the number of rotations by 43%. However, neither change achieved the level of statistical significance (t-test, $p>0.05$). Similar observations with five animals pretreated with 100 nmoles BK showed an 88% increase in latency (but no change in number of rotations); this also was not statistically significant.

Because the BR response did not appear to be acting via a

TABLE 3

EFFECT OF DIFFERENT PRETREATMENTS ON BARREL ROTATION INDUCED BY 20 NMOLES B4162

Inhibitor	Dose†	BR	% Responding	% Control
None	—	21/26	81	(100)
Bradykinin	100	6/8	75	93
Captopril	50	15/28	54	67*
Atropine	1	5/6	83	102
Haloperidol	1	7/7	100	123
Naloxone	10	5/11	45	56*
Phenytoin	100	9/10	90	111
Phenobarbital	50	3/8	38	47*
Diazepam	5	5/12	42	52*
Muscimol	0.2	5/9	56	69
Muscimol	0.5	1/8	13	16*

*Different from control, $p<0.05$ (Fisher's Exact Test).

†Bradykinin and captopril were given ICV 1 min prior to B4162, doses in nmoles; muscimol given ICV 10 min prior to B4162, doses in μg; others given IP 45 min prior (haloperidol) or 30 min prior to B4162, doses in mg/kg.

traditional kinin receptor mechanism, other neurotransmitter receptor antagonists were employed. Atropine, a muscarinic antagonist, and haloperidol, a dopamine antagonist, did not inhibit the response rate to B4162. However, a high dose (10 mg/kg) of naloxone, an opiate antagonist, did cause a significant reduction in response (Table 3). Because of the seizure-like nature of BR behavior, several anticonvulsant drugs were tried. Phenytoin (100 mg/kg) failed to inhibit BR; however, phenobarbital (50 mg/kg) and diazepam (5 mg/kg) both showed a statistically significant inhibition of BR behavior (Table 3). The direct-acting GABA agonist muscimol also showed a significant reduction in BR behavior 10 min after 0.5 μg ICV.

DISCUSSION

The presence of BK in rat brain [9,22] and its ability to elicit specific pharmacological effects upon central administration [7,21] have spurred the search for the CNS function of BK. The synthesis of competitive antagonist analogs of BK [29] provides an important tool in this search. BK effects following ICV administration generally occur in dose ranges of 0.5–5 nmole [7,21]; because BK antagonists have molar potencies several orders of magnitude less than BK [19,29], the first animal was injected with 100 nmole B4162. It began violent barrel rotations within 2 min and died, with a bloody, frothy nasal discharge at 7 min. Subsequently, lower doses were chosen, and only one further acute fatality occurred (with 50 nmole B3600).

The characteristics of this unusual response appear to be quite similar to previous reports with other neuropeptides, including latency time (following lateral ventricle administration), approximate number of rolls, and the overall nature of the movements, including the prerotation limb extensions. Several groups found rotation only in one direction [3,8] whereas most reported rotations in both directions, or did not report the direction. The region near the IVth ventricle, especially the vestibular nuclear complex, has been identified as a probable anatomical locus for this behavior in several studies [2–4, 20]. Unilateral labyrinthectomy also produces BR towards the lesioned side [3], and BR has been suggested to be a model for human dystonia [5,27]. Although BR is a violent motor disturbance, clear electrophysiological evidence of seizure activity associated with BR is lacking [5,11].

The hypothesis that the BR seen in these experiments is produced by blocking a tonically active brain kinin system was tested in several ways. Initial experiments indicated that the response was limited to those peptides with demonstrated kinin antagonist activity, i.e., those containing the DPhe^7 substitution. However, the apparent dose-relationship among the various antagonist analogs at producing BR was different than that reported for blockade of traditional kinin systems [19,29]. For example, B3600 is 10–30 times less potent than B4162 at competing with ^{3}H-BK in binding assays in guinea pig ileum and NIE-115 cell membranes, and furthermore, B4162 antagonizes BK-stimulated phosphatidyl inositol turnover in NIE-115 cells while B3600 is an agonist [19]. Yet the data presented here indicate that both peptides have similar activity, and close to the same potency, at eliciting BR (Table 2). Furthermore, if these analogs were acting via kinin receptor antagonism, one would expect to be able to block their effects by a large dose of BK. However, BK (up to 100 nmole) did not attenuate BR effects of B4162 (Table 3), and in fact this high dose of BK actually produced BR itself in 2 of 10 animals (Table 2). These data argue against mediation of BR by a traditional kinin receptor mechanism. Nevertheless, the structure-activity relationship, which is strongly influenced by DPhe substitution, suggests some kind of receptor-mediated effect.

Peptides containing amino acids with the unnatural D-configuration are often resistant to degradation by peptidases; they may also be more toxic as a result. Another peptide containing the DPhe substitution is [DPro^2, DPhe^7,DTrp^9]substance P. A high dose of 100 nmole induced BR in 1 of 2 rats. D-Phenylalanine itself, however, failed to induce any noticeable behavioral changes up to 100 nmoles. While the DPhe^7 substitution is undoubtedly important in the structure-activity relationship [compare DPhe^{7}BK (B3600) vs. BK], this is apparently due to an effect on the conformation of the peptide rather than any intrinsic toxic activity of the amino acid itself.

The finding that pretreatment with captopril attenuates the BR response to B4162 (Table 3) is surprising. The initial expectation was that it might *enhance* the effect by protecting against degradation by peptidases. It is possible that partial enzymatic degradation by ACE serves to activate the peptides, yielding an "exposed" DPhe on the C-terminal. It is also possible that captopril selectively protects endogenous BK (and/or other neuropeptides) from destruction, which can then counteract the effects of B4162. The DPhe substitution may serve to make B4162 less vulnerable to destruction, and thus the captopril effects would favor the endogenous peptide. The inability of large doses of exogenous BK to protect would seem to argue against this concept, however.

A literature survey reveals that BR pharmacology is not well-understood. Many seemingly unrelated peptides produce BR following ICV administration, including vasopressin [1, 2, 11, 14, 16, 17, 29, 30], oxytocin [2, 16, 17], somatostatin [4, 5, 8, 31], substance P [26] and dynorphin [12, 13, 23] (although many others do not, including thyrotropin releasing hormone, luteinizing hormone releasing hor-

mone, ACTH, αMSH, β-endorphin, Leu- and Met-enkephalin and angiotensin II [6]). Most produce BR only at relatively high doses (>10 nmoles); however, arginine- and lysine-vasopressin are active at doses as low as 1.5–8 ng [6]. Non-peptides can also produce BR, notably chlorpromazine methiodide (CPZMI) [3, 5, 6, 27], as well as bicucculine [15], picrotoxin [3,32], morphine [20], kainic acid [3], and oxotremorine, strychnine and physostigmine [3]. Burke *et al.* [6] claim that BR caused by CPZMI is an anti-muscarinic effect, because it is blocked by carbachol and enhanced by atropine, and because other antimuscarinics (e.g., atropine, propantheline) also elicit BR. Nevertheless, this same group also reports BR following injection of the cholinergic *agonists* oxotremorine and physostigmine directly into the right vestibular nucleus [3]. It is noteworthy that CPZMI injected into this site caused only right rotations (in 6 of 10 animals), whereas the agonists caused only left rotations (in 3 of 13 animals), as did strychnine (4 of 4) and kainic acid (4 of 4). Others have reported that the anti-muscarinics atropine (5 mg/kg) and trihexyphenidyl (10 mg/kg) inhibited BR induced by somatostatin [2,31] and that the dopamine antagonists haloperidol (1 mg/kg) and fluphenazine (9 mg/kg) enhanced BR caused by vasopressin [31]. The involvement of dopamine or muscarinic components in BR produced by the BK analog B4162 seems unlikely, because pretreatment with the muscarinic blocker atropine or with the dopamine antagonist haloperidol had no effect (Table 3).

A high dose of the opiate antagonist naloxone did show significant attenuating effects, suggesting a possible opiate involvement. BR in rats caused by ICV dynorphin 1–13 was blocked by naloxone (10 mg/kg) in one study [23] but not in another [12]. Morphine (45–75 μg) injected into various medullary regions also caused BR, which was not blocked by naloxone (1 mg/kg) [20]. Yet another study found BR following 10 μg ICI 174864 (a selective delta opiate antagonist), and 125 μg DPen^{2,5}-enkephalin (a selective delta agonist) [10]. These data cast some doubt on the opiate nature of the effects observed, and whether the naloxone attenuation seen in this report implies the involvement of opiate receptors. The dose employed (10 mg/kg) was quite high, and naloxone has been shown to interact with other neurochemical systems at such doses, including as a GABA antagonist [28].

Available evidence suggests that BR does not represent an epileptic seizure, but rather a specific motor disturbance mediated by a medullary vestibular mechanism [2–5, 20, 27]. Nevertheless, anticonvulsant drugs have been used successfully to attenuate BR caused by vasopressin. In one study, BR was attenuated by phenytoin (1–200 mg/kg), phenobarbital (50–100 mg/kg), diazepam (5–10 mg/kg) and sodium valproate (125–250 mg/kg) [30]; in another, phenytoin (125 mg/kg) and oxytocin (0.1 μg ICV) were successful [1]. In the present study, diazepam (5 mg/kg) and phenobarbital (50 mg/kg) showed significant attenuation in the number of animals responding, but a high dose of phenytoin (100 mg/kg) had no effect. Benzodiazepines and barbiturates are thought to act at least in part by facilitating GABA neurotransmission, whereas phenytoin probably acts to inhibit seizures via different mechanisms [25]. This suggests that BK analogs somehow act to block tonic GABA inhibition in the medulla (although inhibition by naloxone would seem to argue against this [28]). Support for a GABA role in BR comes from a study that reported BR following two successive injections over six days of bicuculline, a GABA antagonist, into the substantia nigra [15]. The BR response was attenuated by pretreatment with 0.2 μg GABA into the nigra [15]; GABA given ICV does not produce BR [3,6]. The ability of muscimol to attenuate B4162 BR is further evidence of a GABA role in BR (Table 3). Muscimol-treated animals exhibited considerable sedation (one died within 20 min, without exhibiting rotations). Sedation was apparently not required for attenuation of BR behavior, however, because animals treated with diazepam, phenobarbital, haloperidol and phenytoin also appeared sedated, whereas those treated with naloxone did not.

In conclusion, a number of analogs of BK have been shown to produce BR in rats after ICV administration. Only analgos containing a DPhe^7 substitution (which is required for BK antagonist activity) showed activity after a 20 nmole dose. BK itself was weakly active at 100 nmoles, and d-phenylalanine was inactive at 100 nmoles. It is not known whether these peptides are acting as agonists or antagonists. Structure-activity considerations argue against mediation of this effect via traditional kinin systems. Blocking experiments show no involvement with muscarinic or dopamine systems; high dose naloxone, however, will attenuate the response, suggesting possible opiate receptor activation. Finally, inhibition by phenobarbital, diazepam and muscimol, but not phenytoin, imply that these peptides are acting as functional GABA antagonists to disinhibit a GABAergic vestibular control mechanism.

ACKNOWLEDGEMENTS

This work was supported by grant AHA No. 84368 from the DC Capital Affiliate of the American Heart Association. The author wishes to thank Mr. Willie T. Wynn, Ms. Julie Chen and Mr. Yared Aklilu for technical support, Ms. Thu Hoang for manuscript preparation, and Dr. John M. Stewart for supplying the bradykinin analogs.

REFERENCES

1. Abood, L. G., R. Knapp, T. Mitchell, H. Booth and L. Schwab. Chemical requirements of vasopressins for barrel rotation convulsions and reversal by oxytocin. *J Neurosci Res* **5**: 191–199, 1980.
2. Boakes, R. J., J. M. Ednie, J. A. Edwardson, A. B. Keith, A. Sahgal and C. Wright. Abnormal behavioral changes associated with vasopressin-induced barrel rotations. *Brain Res* **326**: 65–70, 1985.
3. Burke, R. E. and S. Fahn. Chlorpromazine methiodide acts at the vestibular nuclear complex to induce barrel rotation in the rat. *Brain Res* **288**: 273–281, 1983.
4. Burke, R. E. and S. Fahn. Studies of somatostatin-induced barrel rotation in rats. *Regul Pept* **7**: 207–220, 1983.
5. Burke, R. E. and S. Fahn. Electroencephalographic studies of chlopromazine methiodide and somatostatin-induced barrel rotation in rats. *Exp Neurol* **79**: 704–713, 1983.
6. Burke, R. E., S. Fahn, H. R. Wagner and M. Smeal. Chlorpromazine methiodide-induced barrel rotation: an antimuscarinic effect. *Brain Res* **250**: 133–142, 1982.
7. Clark, W. G. Kinins and the peripheral and central nervous systems. In: *Bradykinin, Kallidin and Kallikrein. Handbook of Experimental Pharmacology*, Vol 25, Suppl, edited by E. G. Erdos. Berlin: Springer-Verlag, 1979, pp. 311–356.
8. Cohn, M. L. and M. Cohn. "Barrel rotation" induced by somatostatin in the non-lesioned rat. *Brain Res* **96**: 138–141, 1975.

9. Correa, F. M. A., R. B. Innis, G. R. Uhl and S. H. Snyder. Bradykinin-like immunoreactive neuronal systems localized histochemically in rat brain. *Proc Natl Acad Sci USA* **76:** 1489–1493, 1979.
10. Cowan, A., X. Z. Zhu and F. Porreca. Studies *in vivo* with ICI 174864 and DPen^2,DPen^{5}enkepahlin. *Neuropeptides* **5:** 311–314, 1985.
11. Ehlers, C. L., T. K. Reed, M. Wang, C. J. Lebrun and G. F. Koob. EEG effects of subcutaneous and intracerebroventricular injections of arginine vasopressin in the rat. *Psychopharmacology (Berlin)* **87:** 430–433, 1985.
12. Herman, B. H., F. Leslie and A. Goldstein. Behavioral effects and *in vivo* degradation of intracerebroventricularly administered dynorphin-(1–13) and DAla^2-dynorphin-(1–11) in rats. *Life Sci* **27:** 883–892, 1980.
13. Kaneko, T., T. Nakazawa, M. Ikeda, K. Yamatsu, T. Iwama, T. Wada, M. Satoh and H. Takagi. Sites of analgesic action of dynorphin. *Life Sci* **33:** Suppl I, 661–664, 1983.
14. Kastings, N. W., W. L. Veale and K. E. Cooper. Convulsive and hypothermic effects of vasopressin in the brain of the rat. *Can J Physiol Pharmacol* **58:** 316–319, 1980.
15. Kelly, J., G. F. Alheid, A. Newberg and S. P. Grossman. GABA stimulation and blockade in the hypothalamus and midbrain: Effects on feeding and locomotor behavior. *Pharmacol Biochem Behav* **7:** 537–541, 1977.
16. Kordower, J. H. and R. J. Bodnar. Vasopressin analgesia: specificity of action and non-opioid effects. *Peptides* **5:** 747–756, 1984.
17. Kruse, H., TJ. B. VanWimersma Greidanus and D. DeWied. Barrel rotation induced by vasopressin and related peptides in rats. *Pharmacol Biochem Behav* **7:** 311–313, 1977.
18. Mann, J. F. E., R. Boucher and P. W. Schiller. Rotational syndrome after central injection of C-terminal 7-peptide of cholecystokinin. *Pharmacol Biochem Behav* **13:** 125–127, 1980.
19. Manning, D. C., K. M. Braas, D. C. Perry and S. H. Snyder. Bradykinin analogues: differential agonist and antagonist activities. *Eur J Pharmacol*, in press, 1987.
20. Oley, N., C. Cordova, M. L. Kelly and J. D. Bronzino. Morphine administration to the region of the solitary tract nucleus produces analgesia in rats. *Brain Res* **236:** 511–515, 1982.
21. Perry, D. C. Kinins as neuropeptides. In: *Neural and Endocrine Peptides and Receptors*, edited by T. M. Moody. Plenum Press. New York: 1986, pp. 367–387.
22. Perry, D. C. and S. H. Snyder. Identification of authentic bradykinin in mammalian brain. *J Neurochem* **43:** 1072–1080, 1984.
23. Petrie, E. C., S. T. Tiffany, T. B. Baker and J. L. Dahl. Dynorphin (1–13): Analgesia, hypothermia, cross-tolerance with morphine and β-endorphin. *Peptides* **3:** 41–47, 1982.
24. Regoli, D. and J. Barabe. Pharmacology of bradykinin and related kinins. *Pharmacol Rev* **32:** 1–46, 1980.
25. Rall, T. W. and L. S. Schleifer. Drugs effective in the therapy of the epilepsies. In: *Goodman and Gilman's the Pharmacological Basis of Therapeutics*, 7th edition, edited by A. G. Gilman, L. S. Goodman, T. W. Rall and F. Murad. New York: Macmillan Co., 1985, pp. 446–472.
26. Rondeau, D. B., F. B. Jolicoeur, F. Belanger and A. Barbeau. Motor activity induced by substance P in rats. *Pharmacol Biochem Behav* **9:** 769–775, 1978.
27. Rotrosen, J., M. Stanley, C. Kuhn, D. Wazer and S. Gershon. Experimental dystonia induced by quaternary chlorpromazine. *Neurology* **30:** 878–881, 1980.
28. Sawynok, J., C. Pinsky and F. S. LaBella. On the specificity of naloxone as an opiate antagonist. *Life Sci* **25:** 1621–1632, 1979.
29. Stewart, J. M. and R. J. Vavrek. Competitive antagonists of bradykinin. *Peptides* **6:** 161–164, 1985.
30. Wurpel, J. N. D., R. L. Dundore, Y. R. Barbella, C. D. Balaban, L. C. Keil and W. B. Severs. Barrel rotation evoked by intracerebroventricular vasopressin injections in conscious rats. *Brain Res* **365:** 21–41, 1986.
31. Yamada, K., M. Abe, T. Matsuda and T. Furukawa. Barrel rotation induced by vasopressin or somatostatin in rats. *Jpn J Pharmacol* Suppl **39:** 182P, 1985.
32. Zainos, A., R. DeAnda, L. Chaves and M. Garcia-Munoz. Turning behavior, barrel rolling, and sensory neglect induced by picrotoxin in the thalamus. *Exp Neurol* **83:** 534–547, 1984.