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INHIBITION OF VASOPRESSIN RELEASE TO CAROTID OCCLUSION BY γ-AMINOBUTYRIC ACID AND GLYCINE

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1 In cats anaesthetized with pentobarbitone sodium or chloralose, the amino acids, γ-aminobutyric acid (GABA) and glycine, were applied to the ventral surface of the brain stem through paired Perspex rings placed across the medulla.

2 Applied to a region situated at the transition between medulla and cord, both amino acids greatly attenuated and even abolished the vasopressin release in response to carotid occlusion. Glycine was about 100 times more potent than GABA and effective in a concentration of 0.1 mg/ml. The pressor response to carotid occlusion was not affected.

3 Applied to a region situated 5 to 6 mm more rostrally, the amino acids did not affect vasopressin release but in strong concentrations, greatly attenuated the pressor response to carotid occlusion.

4 The two responses to carotid occlusion, vasopressin release and the pressor response, can thus be influenced independently.

5 It is concluded that the pathways carrying afferent impulses from the baroreceptors in the carotid sinus reach the ventral surface of the brain stem at two regions. At both, synaptic transmission can be blocked by the application of an inhibitory amino acid and thus prevent either the release of vasopressin at the caudal site, or the increase of vasomotor tone at the rostral site.

Introduction

A number of drugs release vasopressin in anaesthetized cats when applied to the exposed ventral surface of the brain stem at a region situated bilaterally at the transition between medulla and cervical cord. The first drug shown to have this action was nicotine (Bisset, Feldberg, Guertzenstein & Rocha e Silva Jr, 1975). A similar release was later shown to be caused by tubocurarine, picrotoxin, bicuculline, strychnine and leptazol (Feldberg & Rocha e Silva Jr, 1978). The first four of these five central excitatory substances are known to be antagonists of γ-aminobutyric acid (GABA) and/or of glycine. Leptazol, too, may be a weak antagonist of these amino acids (Hill, Simmonds & Straughan, 1973). It is therefore possible that vasopressin release is continuously inhibited by the activity of GABA and glycine releasing neurones which synapse near the ventral surface of the brain stem and that antagonism of their actions by any of these five central excitatory substances leads to release of vasopressin.

It is well established that afferent inputs from left atrial receptors (Gauer & Henry, 1963; Shade & Share, 1975) as well as from aortic and carotid baroreceptors (Share & Levy, 1962; Clark & Rocha e Silva Jr, 1967) exert a tonic inhibitory reflex control over the release of vasopressin. Removal or reduction of this inhibitory control as, for instance, during bilateral carotid occlusion, results in vasopressin release. If this inhibitory reflex control were to act through glycine and/or GABA releasing interneurones ending at the ventral surface of the brain stem, it should be possible to prevent this release by applying glycine or GABA topically to this surface, i.e. by strengthening the 'amino acid brake'. This possibility was examined in the present experiments.

The vasopressin release produced by the antagonists of GABA and/or of glycine was not associated with blood pressure effects. Nor did the amino acids themselves affect blood pressure when applied to the region of transition between medulla and cervical cord. But when applied to a region situated 5 to 6 mm more rostral at the ventral surface of the brainstem, a different result was obtained. The amino acids produced a fall and their antagonists a rise in blood pressure (Guertzenstein, 1973; Feldberg & Guertzenstein, 1976; Feldberg & Rocha e Silva Jr, 1978). It has been

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suggested that GABA and glycine releasing inhibitory neurones may synapse at this region near the surface of the medulla and be concerned with blood pressure reactions. In the present experiments the effects of the amino acids were examined also when applied to this more rostrally situated region.

Some of the results have been reported to the Physiological Society (Feldberg & Rocha e Silva Jr, 1979).

Methods

Male cats weighing between 2.5 and 3.2 kg were anaesthetized either with chloralose (65 to 75 mg/kg i.v.), or with pentobarbitone sodium (35 mg/kg i.p. and supplemented by 10 mg/kg at the end of the surgical procedures before blood samples were taken). For the injection of the 1% chloralose solution into a cephalic vein, anaesthesia was induced by ethyl chloride.

After cannulating the trachea the cats were artificially ventilated with room air. Arterial blood pressure was recorded from the cannulated right femoral artery. For removing blood samples and replacing them by dextran or by red blood cells suspended in dextran, the right femoral and the right external jugular vein were cannulated. The vagi were divided at the neck and a loose ligature was placed around each common carotid in readiness for bilateral carotid occlusion with arterial clamps.

The method of exposing the ventral surface of the brain stem and of applying the amino acid solution to it through paired Perspex rings placed across the medulla, has been described previously (Feldberg & Guertzenstein, 1972; Guertzenstein, 1973; Bisset *et al.*, 1975). The amino acids were applied to either one or the other of the two bilateral regions marked A and B in the inset of Figure 1. The more rostrally situated region A, lies immediately caudal to the trapezoid bodies, the more caudally situated region B, about 5 to 6 mm more caudal at the transition between medulla and cervical spinal cord. The amino acids were applied in a volume of 20 µl into each ring, replaced every few minutes by fresh solution until washed out after 35 min.

The methods of collecting venous blood samples, centrifuging them, extracting the plasma and assaying the extracts on the water-loaded alcohol anaesthetized rat against arginine vasopressin were those described previously (Bisset *et al.*, 1975). Vasopressin concentrations are expressed as µu/ml plasma.

Materials

Glycine (BDH) and γ-aminobutyric acid (GABA) (BDH) were dissolved in 0.9% w/v NaCl solution (saline) immediately before use.

Results

The resting level of vasopressin in plasma varied in different experiments independently of whether the cats were anaesthetized with pentobarbitone sodium or chloralose. In 27 experiments values between 15 and 191 µu/ml (mean 85 µu/ml) were obtained. In each of these experiments the vasopressin concentration increased when the carotid arteries were occluded for 4 min. The increase varied between 53 and 937% (mean 194%). After releasing the occlusion the vasopressin concentration decreased and in many experiments reached the pre-occlusion level within an hour, but in some it took longer. Further, if the vasopressin concentration was high at the beginning of an experiment it often fell to lower concentrations in the course of a further 1 to 3 h, whether GABA or glycine had, or had not been applied to the ventral surface of the brain stem. These factors explain why the control values for vasopressin given in Tables 1 to 3 under (a) varied in the course of the experiments. To demonstrate the effect of carotid occlusion it was therefore necessary to take the control blood samples shortly before the occlusion (2 min in the present experiments). With this precaution, comparable increases in vasopressin concentrations were obtained when the carotid occlusions were repeated three times at intervals of 1 h or longer whatever the control concentrations were at these times. However, if the increase during the first occlusion had been particularly high, the subsequent increases did not reach the same magnitude. There was no correlation between the magnitude of vasopressin release and the size of the pressor response.

Effect of GABA and glycine on vasopressin release produced by carotid occlusion

GABA and glycine, in concentrations used for testing the vasopressin release produced by carotid occlusion, had little or no effect on the resting level of vasopressin release whether they were applied to the more distal region B, or to the more rostral region A. In six experiments the amino acids were applied in different concentrations (GABA 50 and 100 mg/ml; glycine 0.1 and 20 mg/ml) to the more distal region B for 35 min without producing at the same time a carotid occlusion. In three of these experiments the vasopressin level of the blood rose during the application by 2 to 5%, in the other it fell by 10 to 11%. The effects of the amino acids on the vasopressin release in response to carotid occlusion are summarized in Tables 1 to 3.

Table 1 gives the results of 10 experiments in which GABA was applied to region B. As illustrated in Expts 3 to 10, GABA in concentrations of 10, 50 and 100 mg/ml greatly inhibited and practically abolished

the vasopressin release in response to carotid occlusion. Whereas carotid occlusion increased the vasopressin levels by 53 to 510% (mean 176%) before the application of GABA, the corresponding values obtained during its application were −24 to 56% (mean 15%). In seven of these experiments (Expts 3 to 9), carotid occlusion was retested 30 min and again 90 min after GABA had been removed from the ventral surface. After 30 min the inhibitory effect of GABA was still fully present in one experiment (Expt 8), and had disappeared in another (Expt 9). In the remaining five experiments partial recovery had occurred; the vasopressin levels increased between 20 and 119% (mean 68%) during carotid occlusion. After 90 min there was still partial inhibition in Expt 8, but in the other six experiments the response to carotid occlusion had fully recovered.

No difference was observed between the inhibitory effect of 100, 50 or 10 mg/ml, but 2 mg/ml no longer inhibited the vasopressin release to carotid occlusion. For instance, in Expts 1 and 2 of Table 1 carotid occlusion raised the plasma vasopressin by 95 and 86% before the application of 2 mg/ml of GABA as compared to 108 and 112% during its application, and to 129 and 86% 90 min after its removal.

Table 2 gives the results of 14 experiments with glycine applied to region B. The result was the same whether the cats had been anaesthetized with pentobarbitone sodium or with chloralose. Glycine was effective in about 100 times weaker concentrations than GABA since a concentration of 0.1 mg/ml was found to inhibit the vasopressin release to carotid occlusion (Expts 13 and 14); a concentration of 0.01 mg/ml was subthreshold (Expts 11 and 12). The inhibitory effect was similar whether the glycine was applied in a concentration of 0.1, 0.5, 2, 10 or 50 mg/ml. The vasopressin release in response to carotid occlusion was abolished, or nearly abolished. In Expts 13 to 23, the control carotid occlusions increased the vasopressin concentrations of plasma by 56 to 602% (mean 176%); during application of the various glycine concentrations the corresponding figures were −13 to 58% (mean 18%). In nine of these experiments carotid occlusion was retested 30 min after removal of glycine; in two experiments there was still full inhibition (Expts 18 and 21) and in only two (Expts 14 and 20) had full recovery occurred; but 90 min after removal recovery had occurred in most experiments.

In the last experiment of Table 2 (Expt 24) the sequence was different in that the carotid occlusion during application of glycine was not preceded by a control carotid occlusion. The result was the same as in the other experiments: inhibition of vasopressin release during the glycine application.

Table 3 gives the results of five experiments in which either GABA or glycine were applied to region A in concentrations which, applied to region B, would have inhibited the vasopressin release in response to carotid occlusion. But applied to region A, they caused no such inhibition; in each of the five experiments the carotid occlusion carried out during this application produced strong release of vasopressin.

Table 1 Effect in anaesthetized cats of γ-aminobutyric acid (GABA) applied for 35 min to the ventral surface of the brain stem at the region marked B in the inset of Figure 1 on vasopressin release produced by 4 min bilateral carotid occlusion

		I *Before GABA application*			II *During GABA application*		III *30 min after GABA removal*		IV *90 min after GABA removal*	
Expt No.	*GABA* (mg/ml)	(a)	(b)	(c)	(a)	(b)	(a)	(b)	(a)	(b)
1	2	116	226 (95)	139	100	205 (105)	—	—	104	238 (129)
2	2	98	182 (86)	99	74	157 (112)	—	—	96	179 (86)
3	10	105	236 (125)	94	81	106 (30)	74	140 (89)	85	248 (192)
4	10	177	270 (53)	151	76	79 (4)	61	74 (21)	67	124 (85)
5	10	110	227 (106)	127	93	91 (−2)	95	115 (20)	66	137 (108)
6	50	101	293 (191)	127	88	67 (−24)	99	218 (119)	97	259 (167)
7	50	39	91 (136)	48	44	49 (12)	44	85 (89)	56	165 (196)
8	100	36	220 (510)	101	54	84 (56)	41	67 (57)	44	96 (119)
9	100	102	228 (123)	98	58	62 (6)	52	137 (163)	65	211 (224)
10	100	79	208 (163)	99	52	70 (36)	—	—	—	—

The figures in columns I to IV refer to plasma vasopressin concentrations in μu/ml from blood obtained (a) 2 min before, (b) during the 4th min of, and (c) 60 min after carotid occlusion. The figures in parentheses give percentage increases (or decreases) during the occlusions. The intervals between Ic and IIa varied between 45 and 90 min. Expts 1 to 9 pentobarbitone sodium, Expt 10 chloralose anaesthesia.

Effect of GABA and glycine on pressor response produced by carotid occlusion

When applied to region B, glycine had scarcely any effect on arterial blood pressure (Feldberg & Guertzenstein, 1976). This finding was confirmed and extended in the present experiments to GABA. It was further found that neither amino acid had any effect on the pressor response to bilateral carotid occlusion even when applied to this region in concentrations of 100 mg/ml for GABA and of 50 mg/ml for glycine.

Both amino acids were previously shown to lower arterial blood pressure when applied to region A and for glycine it was further shown that the blood press-

Table 2 Effect in anaesthetized cats of glycine applied for 35 min to the ventral surface of the brain stem at the region marked B in the inset of Figure 1, on vasopressin release produced by 4 min bilateral carotid occlusion

		I *Before glycine application*			II *During glycine application*		III *30 min after glycine removal*		IV *90 min after glycine removal*	
Expt No.	*Glycine* (mg/ml)	(a)	(b)	(c)	(a)	(b)	(a)	(b)	(a)	(b)
11	0.01	59	121 (105)	59	51	105 (106)	—	—	66	132 (100)
12	0.01	89	271 (204)	91	67	128 (91)	49	95 (94)	61	120 (97)
13	0.1	98	233 (138)	135	135	186 (38)	104	183 (76)	112	211 (88)
14	0.1	191	364 (91)	126	113	130 (15)	120	240 (100)	114	240 (111)
15	0.5	143	223 (56)	110	79	78 (−1)	61	81 (33)	63	115 (82)
16	2.0	87	230 (164)	63	42	55 (30)	55	87 (58)	71	184 (159)
17	10	104	236 (127)	93	88	105 (19)	79	135 (71)	47	143 (204)
18	50	115	297 (159)	113	104	99 (−5)	86	98 (14)	72	92 (19)
19	50	42	112 (167)	—	80	98 (22)	89	170 (91)	54	163 (219)
20	50	44	110 (150)	—	53	84 (58)	56	176 (214)	45	153 (240)
21	50	15	40 (167)	—	22	23 (5)	24	28 (17)	20	72 (260)
22	50	54	119 (120)	73	75	88 (17)	—	—	71	138 (94)
23	50	46	323 (602)	—	38	33 (−13)	—	—	24	41 (71)
24	50	—	—	—	85	108 (27)	—	—	95	190 (102)

The figures in columns I to IV refer to plasma vasopressin concentrations in μu/ml from blood obtained (a) 2 min before, (b) during the 4th min of, and (c) 60 min after carotid occlusion. The figures in parentheses give percentage increases (or decreases) during the carotid occlusions. The intervals between Ic and IIa varied between 45 and 90 min. Expts 11 to 18 pentobarbitone sodium, Expts 19 to 24 chloralose anaesthesia.

Table 3 Effect in cats anaesthetized with pentobarbitone sodium of γ-aminobutyric acid (GABA) or glycine applied for 35 min to the ventral surface of the brain stem at the region marked A in the inset of Figure 1, on vasopressin release produced by 4 min bilateral carotid occlusion

		I *Before amino acid application*			II *During amino acid application*		III *90 min after amino acid removal*	
Expt No.	*GABA* (mg/ml)	(a)	(b)	(c)	(a)	(b)	(a)	(b)
25	25	73	140 (92)	113	75	131 (75)	63	115 (82)
	Glycine (mg/ml)							
26	2	101	247 (144)	141	107	245 (129)	81	153 (89)
27	10	25	259 (937)	100	61	364 (497)	60	371 (518)
28	50	53	187 (253)	75	62	135 (118)	—	—
29	50	—	—	—	120	309 (158)	143	302 (111)

The figures in columns I to III refer to plasma vasopressin concentrations in μu/ml from blood obtained (a) 2 min before, (b) during the 4th min of, and (c) 90 min after carotid occlusion. The figures in brackets give percentage increases during-the carotid occlusions. The intervals between Ic and IIa varied between 45 and 90 min.

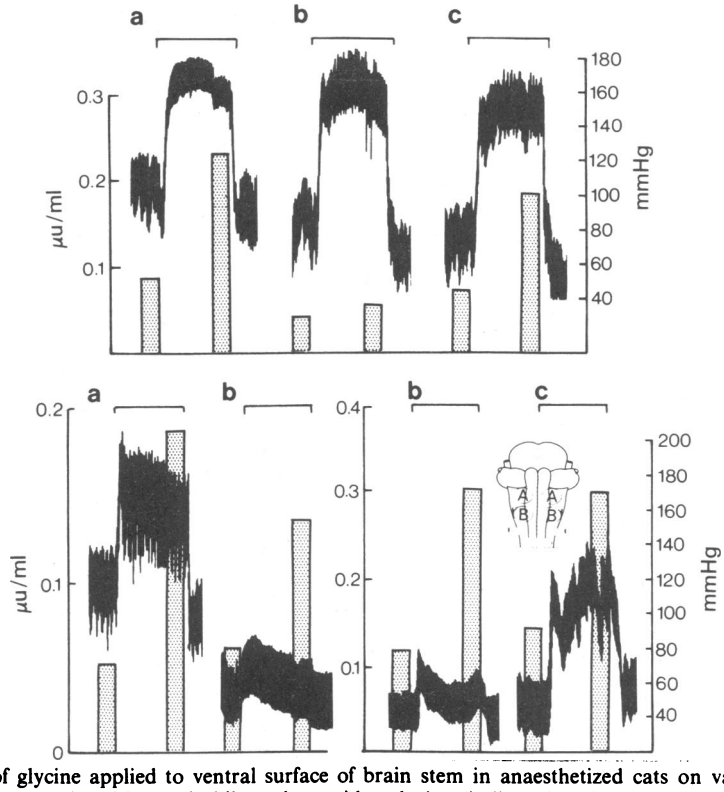

Figure 1 Effect of glycine applied to ventral surface of brain stem in anaesthetized cats on vasopressin release and pressor response produced by 4 min bilateral carotid occlusion (indicated by horizontal bars). Carotid occlusion before (at a), during (at b), and after (at c) glycine application. The vertical columns beneath each blood pressure tracing indicate plasma concentration of vasopressin in blood samples collected before and during the 4th min of carotid occlusion. Intervals between (a) and (b), and between (b) and (c), 90 min. Top records from a 2.6 kg cat (Expt 16 of Table 2). Application of 2 mg/ml glycine to region B. Bottom records: the two left ones from a 2.9 kg cat (Expt 28 of Table 3), and two right ones from a 3.2 kg cat (Expt 29 of Table 3). Application of 50 mg/ml glycine to region A. Ordinates: vasopressin concentration in μu/ml. Arterial blood pressure in mmHg. Inset: diagram of ventral surface of brainstem with regions A and B indicated by marked ovals.

ure lowering area within region A was not larger than 1.5 mm^2 (Guertzenstein, 1973; Guertzenstein & Silver, 1974). In the present experiments both amino acids were found not only to lower arterial blood pressure when applied to region A, but also greatly to attenuate the pressor response to carotid occlusion when applied in high concentrations (GABA 50 and 100 mg/ml; glycine 25 and 50 mg/ml). This was found to occur in all six experiments in which the amino acids were applied in such concentrations to this region, and is illustrated for glycine in the bottom records of Figure 1.

When applied to the ventral surface of the brain stem, the two amino acids thus inhibit both the pressor response and the vasopressin release to carotid occlusion but the two responses were affected from different regions, the pressor response from region A, and the vasopressin release from region B. This difference is illustrated for glycine in Figure 1. The upper portion illustrates the attenuation of the vasopressin release to carotid occlusion during application of 2 mg/ml glycine to region B, without attenuation of the pressor response which, in this experiment was slightly greater than before or after the glycine application. The lower portion illustrates in two experiments the greatly reduced pressor response to carotid occlusion but with a strong release of vasopressin during application of 50 mg/ml of glycine to region A. The reduction in the pressor response can, to a small extent only, be accounted for by the fall in blood pressure; for instance, in Expt 29, the pressor response recovered after removal of the glycine, whilst blood pressure was still low.

Discussion

The finding that antagonists of GABA and glycine release vasopressin when applied to the ventral sur-

face of the brain stem suggested that vasopressin release may be continuously inhibited by GABA and glycine-releasing neurones which synapse near this surface, that nervous influences which release vasopressin might do so by removing this 'amino acid brake' and that such release may be prevented by strengthening the brake, i.e. by applying GABA or glycine to the amino acid-sensitive region (Feldberg & Rocha e Silva Jr, 1978). These suggestions were borne out by the finding that GABA and glycine inhibited the vasopressin release to carotid occlusion.

According to Curtis (1974) 'glycine and GABA can be considered as major central inhibitory transmitters in the mammal, the former in the regulation of spinal and brain stem reflexes, the latter mainly in supraspinal regions but also in the cord'. The region where the amino acids act when inhibiting vasopressin release is at the transition of medulla and spinal cord, and the transmitter for this function may be mainly glycine. This could explain its greater potency. Another explanation might be that glycine is the sole inhibitory transmitter and that the glycine receptors have some sensitivity to GABA as well (Curtis, Hösli & Johnston, 1968), or that the GABA releasing neurones synapse in this region at some distance from the ventral-surface.

Application of hexamethonium to the region where the amino acids act, inhibits the vasopressin release produced by nicotine similarly applied but not the release in response to carotid occlusion (Bisset & Feldberg, 1977). This would suggest that the nicotine-sensitive synapses do not lie in the pathway of the carotid occlusion reflex for vasopressin release. The synapses at which the amino acids exert their inhibitory effect on vasopressin release, on the other hand, would appear to lie in the pathway of this neurosecretory reflex arc, and the fact that the amino acids did not affect vasopressin release in the absence of carotid occlusion might suggest that in this condition the amino acids exert their maximal inhibitory effects. It would be interesting to know whether hexamethonium affects the vasopressin release produced by GABA and glycine antagonists, and whether the amino acids affect the vasopressin release in response to nicotine.

One possible arrangement of neuronal connections between the afferent input from the sinus nerves and the neurohypophysis is given diagrammatically in Figure 2. The afferent fibres of the sinus nerves terminate in the rostral part of the nucleus tractus solitarius (Smith & Pearce, 1961; Jordan & Spyer, 1977). Evidence for nervous connections between this region and region B at the ventral surface has been obtained in cats by two methods. Loewi & Burton (1978) injected [^{3}H]-proline and [^{3}H]-leucine into a portion of the nucleus tractus solitarius from which cardiac activity could be recorded, and traced the 'antero grade' transported amino acids in nerve fibres to many parts of the brain stem and spinal cord including the area corresponding to region B. Errington & Dashwood (1979) applied horseradish peroxidase with Perspex rings to the ventral surface at region B and traced the enzyme 'retrograde' along nerve fibres to cell bodies in the rostral part of the nucleus of the tractus solitarius. In Figure 2, the neuronal connections between the carotid sinus and region B, are shown by continuous lines, the connection between this region and the supraoptic nucleus by a dotted line, in order to indicate that such a connection, though it must exist, has not been demonstrated.

The suggestion that GABA and glycine-releasing inhibitory neurones which synapse at the more rostral region of the ventral surface are concerned with blood pressure reactions (Feldberg & Rocha e Silva Jr, 1978) is borne out by the finding that GABA and glycine applied to this region inhibit the pressor response to carotid occlusion. The fact that strong concentrations were required for both amino acids to produce this inhibition may signify that to reach the sensitive synapses, the amino acids have to penetrate the brain tissue some distance and on their way are subjected to the action of destroying enzymes. The inhibitory effect on the pressor response was not known but Dashwood & Feldberg (1977) observed that GABA not only lowered blood pressure but also greatly attenuated the pressor response to carotid occlusion when injected into a lateral ventricle of anaesthetized cats. In these experiments the GABA probably acted also on the ventral surface of the brain stem because the effects no longer occurred when the aqueduct had been cannulated and GABA was thus prevented from entering the subarachnoid space (unpublished experiments).

The central connections responsible for the pressor response to carotid occlusion are complex and controversial (see Kirchheim, 1976). In rats, the reflex can, after aortic arch denervation, be integrated entirely at a medullary level (Lopes, Cipola-Neto & Rocha e Silva Jr, 1977). Region A appears to lie on a distal part of the efferent pathway of the reflex, a suggestion supported by a recently described anatomical connection between region A and the intermediolateral nucleus in the thoracic cord from where the sympathetic vasomotor efferents arise (Amendt, Czachurski, Dembowsky & Seller, 1978).

Our results suggest that the afferent impulses arising from the baroreceptors in the carotid sinus reach the ventral surface of the brain stem, whatever central synapses they have crossed on their way. Here they synapse either at the region of transition between medulla and cord, or 5 to 6 mm more rostral. At both regions the synaptic transmitter would appear to be an inhibitory amino acid but when released, it serves different functions: inhibition of vasopressin release at

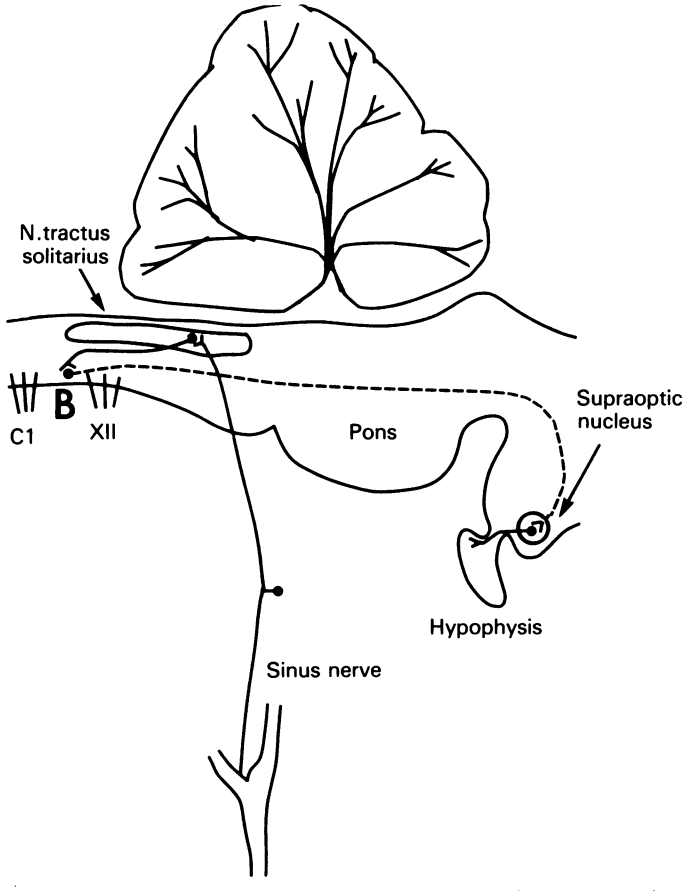

Figure 2 Diagram illustrating possible neuronal connections between sinus nerve, region B and neurohypophysis.

the caudal, and inhibition of sympathetic tone to blood vessels and heart at the rostral region. Carotid occlusion, which removes the afferent impulses, removes the 'amino acid brake' at both regions, consequently vasopressin is released and blood pressure rises with an increase in heart rate.

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