ELSEVIER

European Journal of Pharmacology 285 (1995) 299–304

ejp

Evidence against the involvement of the nucleus tractus solitarii in the sympatholytic effect of 8-hydroxy-2-(di-*n*-propylamino)tetralin in the cat

C. Vayssettes-Courchay, F. Bouysset, T.J. Verbeuren *, M. Laubie

Servier Research Institute, Department of Angiology, 11, Rue des Moulineaux, 92150 Suresnes, France

Received 18 May 1995; revised 6 July 1995; accepted 11 July 1995

Abstract

In different animal species, microinjections of the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) into the nucleus tractus solitarii failed to alter arterial blood pressure and sympathetic nerve activity; however, the cardiovascular effects (hypotension, bradycardia, reduction in sympathetic nerve activity) of intravenous administration of 8-OH-DPAT were significantly reduced after blockade of the nucleus tractus solitarii by kainic acid as well as after blockade of the lateral tegmental field by kainic acid. The aim of the present study was to clarify these conflicting results. In the anesthetized cat, inhibition of neurotransmission in the nucleus tractus solitarii by bilateral microinjections of either muscimol (1 nmol in 50 nl) or kynurenic acid (2.5 nmol in 50 nl) suppressed the baroreceptor reflex and abolished the synchronism between the renal sympathetic bursts; however, these procedures did not alter the dose-related hypotension, bradycardia and sympatho-inhibition elicited by cumulative doses of 8-OH-DPAT (1–30 μg/kg i.v.). Moreover complete electrolytic destruction of the nucleus tractus solitarii, assessed by a complete loss of the baroreceptor reflex and the cardiac-related bursts of the sympathetic nerves, failed to alter the inhibitory effects of i.v. 8-OH-DPAT. Bilateral microinjections of muscimol into the lateral tegmental field induced a decrease of mean arterial blood pressure, heart rate and renal nerve activity (by respectively -35 ± 13 mm Hg, -30 ± 16 beats/min and $-53 \pm 14\%$) and greatly reduced the effects of subsequent i.v. administration of 8-OH-DPAT. The present data indicate that the nucleus tractus solitarii does not play a dominant role in the central action of 8-OH-DPAT whereas they confirm our previous results showing that the lateral tegmental field is involved in this action and in the mecanisms regulating sympathetic tone. The results also suggest that kainic acid lesions are not restricted to the region in which the neurotoxic agent is injected.

Keywords: 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin); Nucleus tractus solitarii; Lateral tegmental field; Muscimol; Kynurenic acid

1. Introduction

The 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin, 8-OH-DPAT (Middlemiss and Fozard, 1983) produces dose-related hypotension and bradycardia in rats, cats and dogs by acting at the level of the medulla. Indeed, the decreases in blood pressure and heart rate are associated with inhibition of the activity of several sympathetic nerves (McCall et al., 1987; Ramage and Fozard, 1987; Laubie et al., 1989) and methiothepine injected into the vertebral artery can prevent the sympatho-inhibitory effect of 8-OH-DPAT administered by the same route (Laubie et al., 1989). Several studies have been performed to localize the site(s) of action of 8-OH-DPAT. The 5-HT neurons and the cardiovascular neurons of the raphe nuclei do not appear to be essential (Laubie et al., 1989; McCall et al., 1989; King and McCall, 1991) whereas the cardiovascular neurons of both the rostral ventrolateral medulla and the lateral tegmental field have been implicated in the sympatho-inhibitory action of 8-OH-DPAT, as demonstrated by unit recordings or microinjection studies (Laubie et al., 1989; King and Holtman, 1990; Clement and McCall, 1990, 1992; Mandal et al., 1991; Nosjean and Guyenet, 1991; Wang and Lovick, 1992; Vayssettes-Courchay et al., 1993a). We have previously reported that microinjections of kainic acid into the nucleus tractus solitarii produced hyper-

* Corresponding author. Tel. (33.1.) 41.18.25.18, fax (33.1.) 41.18.24.30.

SSDI 0014-2999(95)00423-8

tension, tachycardia and sympatho-excitation in anaesthetized cats (Vayssettes-Courchay et al., 1993b) and that subsequent i.v. administration of 8-OH-DPAT failed to produce its usual dose-related hypotension, bradycardia and sympatho-inhibition. On the other hand, microinjections of 8-OH-DPAT into the nucleus tractus solitarii did not modify blood pressure, heart rate and sympathetic activity in intact anaesthetized cats (Vayssettes-Courchay et al., 1993b). Moreover, the central sympatho-inhibitory effects of 8-OH-DPAT were not altered by peripheral baroreceptor denervation (King and McCall, 1991; Laubie et al., 1989). A re-examination of the role of the nucleus tractus solitarii in the central sympatho-inhibitory effect of 8-OH-DPAT seems justified considering these conflicting results. The nucleus tractus solitarii and the rostral ventrolateral medulla are strongly connected through the caudal ventrolateral medulla to form the central pathway of the baroreflex in which excitatory amino acids are involved as neurotransmitters. It was shown that the caudal ventrolateral medulla was not necessary for the central action of the 8-OH-DPAT (Vayssettes-Courchay et al., 1993b). But at the same time, the lateral tegmental field was suggested to play a role in the medullary baroreflex pathway (Vayssettes-Courchay et al., 1993a; Clement and McCall, 1993b). We consequently suggested that 8-OH-DPAT acted on an efferent baroreceptor reflex pathway involving the nucleus tractus solitarii, the lateral tegmental field and the rostral ventrolateral medulla. The present study was performed to test this hypothesis, by blocking neurotransmission into the nucleus tractus solitarii by other means (electrolytic lesions, microinjections of muscimol or kynurenic acid) than microinjections of the excitotoxic agent, kainic acid.

2. Material and methods

The experiments were performed as described previously (Vayssettes-Courchay et al., 1993a,b). Cats of either sex weighing 2.8–3.6 kg were anaesthetized with pentobarbital 30 mg/kg i.p. as initial dose and continuous infusion of 4 mg/kg/h i.v. Artificial ventilation was performed with a Harvard respirator. End tidal CO_2 was held near 4% (micro-capnometer, Columbus Inst.) and body temperature was maintained at 38°C. Arterial blood pressure was measured with a Millar pressure transducer in the femoral artery. A femoral vein was cannulated for intravenous drug administration. The renal nerve was exposed by a retroperitoneal approach, dissected free and placed on a bipolar platinium electrode (diameter 0.08 mm). The nerve signal was amplified (DAM 60 WPI) with a band pass of 300 Hz–1 kHz and measured (μV/s) with a Gould integrator. The level of noise was recorded at the end of the experiment after application of xylocaine 5% on the nerve. The control value of renal nerve activity was defined as 100% after subtraction of the noise. The arterial blood pressure, the heart rate, the electrocardiogram (ECG) and the renal nerve activity were recorded on a magnetic tape and displayed on a Gould ES1000 recorder. The post R wave average of renal sympathetic nerve discharge and blood pressure was analyzed on line, using a Compaq 386s computer coupled with a CED 1401 laboratory interface system unit and SPIKE 2 software (CED). The cats were placed in a stereotaxic frame. The fourth ventricule was exposed by opening the posterior fossa. Using a dorsal approach 3 bilateral microinjections were made into the nucleus tractus solitarii or the lateral tegmental field. In other experiments, 3 or 4 bilateral electrolytic lesions of the nucleus tractus solitarii were made (1 mA during 20 s) with a monopolar stainless steel electrode, tip diameter 0.1 mm. The nuleus tractus solitarii was reached between 0.5 mm caudal to the obex and 2.5 mm rostral to the obex, 2–2.5 mm laterally and 1.3 mm beneath the dorsal surface. The lateral tegmental field was reached 1–3 mm rostral to the obex, 2.5–3 mm laterally and 3.5 mm beneath the dorsal surface. The microinjections were made from a glass micropipette (tip diameter 10 μm) held in a micromanipulator, using a WPI nanopump. The drugs were dissolved in artificial cerebrospinal fluid with 1% of fast green, and injected in 50 nl. The drugs used were: kynurenic acid (Sigma), 50 mM, pH: 7.22, 236 mOsm/kg; muscimol (Sigma), 20 mM, pH: 8.02, 330 mOsm/kg. The activation of the baroreflex was performed by slow intravenous administration of 5 μg/kg i.v. *l*-phenylephrine. In each experiment, the post-R wave average of arterial blood pressure and renal nerve activity and the response of the nerve activity to the baroreflex activation were tested before and after the microinjections or the lesions. 8-OH-DPAT was administered intravenously in cumulative doses at 1, 3, 10, 30 μg/kg. At the end of the experiments, the brain stem was removed and 20 μm coronal sections were cut on a cryostat and counterstained with thionine to identify the nuclei and localize the sites of injections or lesions. The data were analyzed with the 1401 unit system and the SPIKE 2 software (CED) and were expressed as means ± S.E.M. Student's *t*-test for paired or unpaired comparisons was used to assess the statistical significance of the results.

3. Results

3.1. Effects of i.v. 8-OH-DPAT

In four intact anaesthetized cats, 8-OH-DPAT was administred at cumulative doses (1, 3, 10, 30 μg/kg

i.v.) and the values of mean blood pressure, heart rate and renal sympathetic nerve activity were recorded at maximal effect (4 min after i.v. administration). The basal value for mean blood pressure was 137 ± 14 mm Hg, heart rate was 177 ± 10 beats/min and the renal nerve activity was taken as 100%. After 30 μg/kg i.v. 8-OH-DPAT, the decrease of mean blood pressure was −49 ± 12 mm Hg, heart rate decreased by −73 ± 11 beats/min and renal nerve activity was reduced (−86 ± 7%).

3.2. Effect of 8-OH-DPAT after microinjections of kynurenic acid into the nucleus tractus solitarii

In five experiments, three bilateral microinjections of kynurenic acid (2.5 nmol in 50 nl) produced neither immediate nor delayed effects on mean blood pressure, heart rate or renal sympathetic activity. Before the microinjections of kynurenic acid, mean blood pressure was 139 ± 5 mm Hg and heart rate 191 ± 6 beats/min. Ten minutes after kynurenic acid, mean blood pressure was 136 ± 8 mm Hg and heart rate was 193 ± 9 beats/min; renal nerve activity was not altered (100 versus 93 ± 12%). However, the correlation between the renal nerve activity and the ECG and the sympatho-inhibition produced by activation of the baroreflex elicited by *l*-phenylephrine (5 μg/kg i.v.) had disappeared. Subsequent intravenous administration of 8-OH-DPAT in cumulative doses induced decreases in mean blood pressure, heart rate and renal sympathetic nerve activity comparable with the decreases recorded in intact animals. At the maximal dose of 8-OH-DPAT (30 μg/kg i.v.), mean blood pressure decreased by −31 ± 3 mm Hg, heart rate was reduced by −62 ± 10 beats/min and renal nerve activity was decreased by −75 ± 11% (Fig. 2).

Two additional experiments were performed in order to determine the duration of the action of kynurenic acid on neurotransmission in the nucleus tractus solitarii. Forty minutes after the microinjections of kynurenic acid, the baroreflex and the synchronisation between the renal nerve activity and the heart rate were still abolished.

3.3. Effect of 8-OH-DPAT after microinjections of muscimol into the nucleus tractus solitarii

In four experiments, the basal value for mean blood pressure was 140 ± 14 mm Hg, heart rate was 191 ± 16 beats/min and renal nerve activity was taken as 100%. Three bilateral microinjections of muscimol (1 nmol in 50 nl) were made into the nucleus tractus solitarii. These microinjections of muscimol did not significantly change mean blood pressure, heart rate and renal sympathetic nerve activity. However, the correlation between the renal nerve activity and the R wave of the ECG had disappeared after the last microinjection of muscimol. Furthermore the hypertensive response to i.v. phenylephrine (5 μg/kg) no longer inhibited the renal sympathetic discharge (Fig. 1). These inhibitory effects of muscimol were still present after 40 min (two experiments). In the four experiments described above, 8-OH-DPAT was administered i.v. at cumulative doses, 5–10 min after the last microinjection of muscimol into

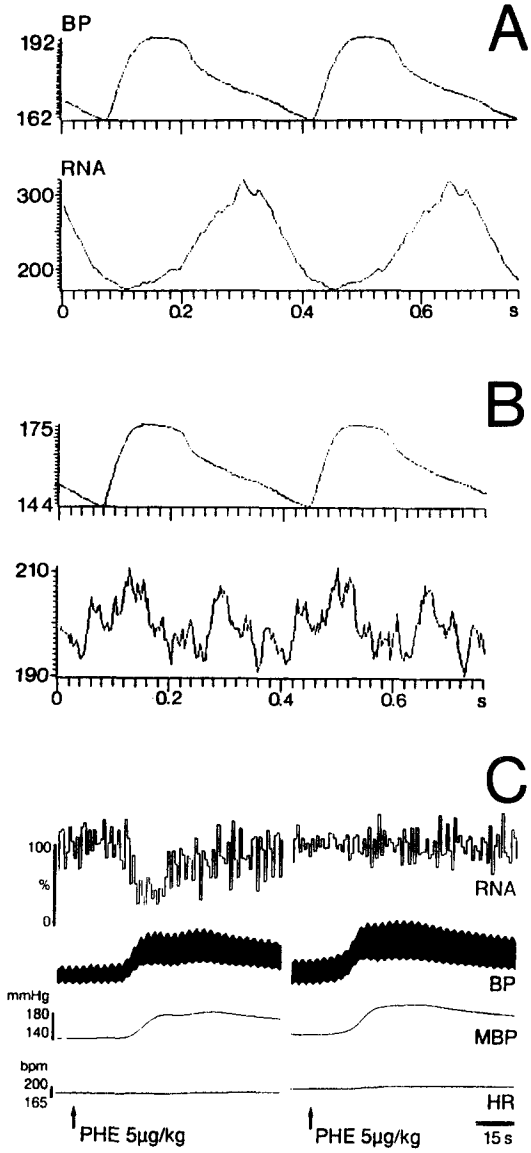

Fig. 1. Typical example of the results obtained after microinjection of muscimol into the nucleus tractus solitarii. (A) Before the injection of muscimol, a correlation exists between cardiac rhythm (upper panel) and renal nerve activity (lower panel). (B) After the microinjection of muscimol, the correlation has disappeared. (C) Left panel: Sympatho-inhibition due to the baroreceptor reflex activation caused by i.v. injection of *l*-phenylephrine. Right panel: After the microinjection of muscimol, the sympatho-inhibition has disappeared. BP = blood pressure, PHE = *l*-phenylephrine, MBP = mean blood pressure, bpm = beats per minute, HR = heart rate, RNA = renal nerve activity.

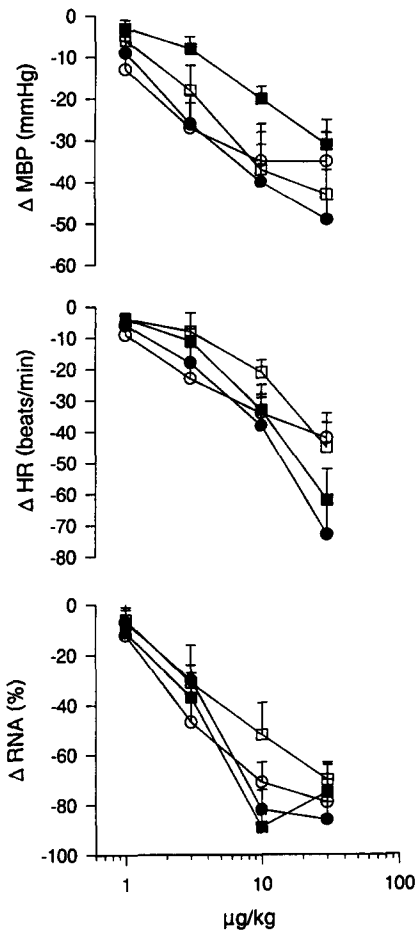

Fig. 2. Effects of 8-OH-DPAT (1–30 μg/kg i.v.) on mean blood pressure (MBP; upper panel), heart rate (HR; middle panel) and renal sympathetic nerve activity (RNA; lower panel) in the control group (●), after kynurenic acid microinjections into the nucleus tractus solitarii (■), after muscimol microinjections into the nucleus tractus solitarii (○) and after electrolytic lesions of the nucleus tractus solitarii (□). The three procedures did not significantly alter the hypotension, the bradycardia and the sympatho-inhibition caused by 8-OH-DPAT.

the nucleus. The dose-response curves of 8-OH-DPAT were not altered. After 30 μg/kg i.v., mean blood pressure decreased by −35 ± 10 mm Hg, heart rate was reduced by −42 ± 8 beats/min and the reduction of renal sympathetic nerve activity was −79 ± 9%. These values were similar to the values recorded in intact animals (Fig. 2).

3.4. Effect of 8-OH-DPAT after electrolytic lesions of the nucleus tractus solitarii

Four bilateral electrolytic lesions were made in five experiments. Each lesion into the nucleus tractus solitarii produced a transient hypertension (+30 ± 3 mm Hg) and a tachycardia (+12 ± 2 beats/min). Ten minutes after the last lesion, mean blood pressure was 136 ± 1 versus 146 ± 11 mm Hg and heart rate was 207 ± 11 versus 193 ± 11 beats/min. Renal nerve activity was not altered. As expected, the correlation between renal sympathetic nerve activity and the ECG had disappeared and phenylephrine failed to produce renal sympatho-inhibition.

Subsequent i.v. administration of 8-OH-DPAT produced dose-dependent hypotension, bradycardia and sympatho-inhibition, with values not significantly different from those recorded in intact animals. At the highest dose used (30 μg/kg i.v. 8-OH-DPAT), mean blood pressure decreased by −43 ± 11 mm Hg, heart rate was reduced by −45 ± 8 beats/min and renal sympathetic nerve activity decreased by −70 ± 7% (Fig. 2).

3.5. Microinjections of muscimol into the lateral tegmental field

No significant changes in mean blood pressure, heart rate and renal nerve activity were observed immediately after the first microinjection of muscimol (20 mM, 80 nl) into the lateral tegmental field whereas 1 min later, MBP, HR and RNA started to decrease and then progressively decreased as further injections were made. After the last microinjection, the levels of MBP and HR were significantly lower: 94 ± 9 versus 129 ± 8 mm Hg, 156 ± 3 versus 186 ± 16 beats/min as compared to those noted before the first injection and the RNA was decreased to 47 ± 14% ($n = 4$). The correlation between RNA and the R wave was strongly reduced in two cats and abolished in the two other cats. The baroreflex activation by *l*-phenylephrine failed to inhibit RNA. Blood pressure, heart rate and RNA were not affected by subsequent i.v. administration of increasing doses of 8-OH-DPAT. The values of blood pressure, heart rate and RNA after the higher dose of 8-OH-DPAT (30 μg/kg) were 94 ± 6 mm Hg, 148 ± 4 beats/min and 48 ± 11%. However, the levels of MBP, HR and RNA before injection of 8-OH-DPAT were significantly lower than in the groups of cats described above.

4. Discussion

We have previously shown that kainic acid lesions of the nucleus tractus solitarii abolished the central sympatho-inhibitory and hypotensive effect of 8-OH-DPAT (Vayssettes-Courchay et al., 1993b) as had been previously demonstrated for the lateral tegmental field, using the same excitotoxic amino acid (Clement and McCall, 1993a; Vayssettes-Courchay et al., 1993a). The conclusion of these previous studies, that the nucleus tractus solitarii is involved in the central sympatholytic effect of 8-OH-DPAT, is not supported by the present

experiments. Indeed, the blockade of neurotransmission in the nucleus by the GABA agonist muscimol or the excitatory amino acid antagonist kynurenic acid failed to alter the dose-dependent hypotension, bradycardia and sympatho-inhibition elicited by i.v. 8-OH-DPAT. It is well established that GABA acts as an inhibitory transmitter substance within the nucleus tractus solitarii (Bennett et al., 1987) and it has been reported that microinjections of kynurenic acid into the intermediate portion of the nucleus tractus solitarii blocked the baroreceptor reflexes and inhibited the temporal correlation between sympathetic nerve activity and heart rate in the cat (Gebber et al., 1989). Also, extensive electrolytic destruction of the nucleus tractus solitarii had no effect on the sympatholytic effect of 8-OH-DPAT. These results fit in well with the fact that peripheral baroreceptor denervation did not modify the central sympatho-inhibitory effect of the drug (King and McCall, 1991; Laubie et al., 1989) and that microinjections of 8-OH-DPAT into the nucleus tractus solitarii failed to alter blood pressure, heart rate or sympathetic nerve activity in both dogs and cats (Laubie et al., 1989; Vayssettes-Courchay et al., 1993b).

Thus while the data presented in our study demonstrate that the nucleus tractus solitarii is not directly involved in the central action of 8-OH-DPAT, they raise three points which have to be clarified: (1) the effect of microinjection of kynurenic acid and muscimol into the nucleus tractus solitarii, (2) the previously reported effects of kainic acid lesions into the nucleus tractus solitarii, and (3) the role of the lateral tegmental field.

As could be expected, the manipulations performed in order to block neurotransmission into the nucleus tractus solitarii abolished the sympathetic inhibition due to baroreceptor reflex activation. Similar results have been reported in the rat (Talman, 1989; Leone and Gordon, 1989; Verberne and Guyenet, 1992). Moreover, the correlation between the renal nerve activity and the R wave disappeared, which is in agreement with the studies of Barman and Gebber (1980) showing that the correlation depends on the integrity of the baroreceptor reflex. These observations then provide evidence indicating that a complete blockade of neurotransmision was obtained with the procedures used. Despite this blockade, mean blood pressure, heart rate and RNA were not significantly modified by these different manipulations, in contrast to data that have been reported in the literature. These divergent data can theoretically be explained by either species differences or, perhaps more likely, by differences in the injection site. Indeed in the rat microinjections of kynurenic acid into the nucleus tractus solitarii produced either weak or profound hypertension (Guyenet et al., 1987; Leone and Gordon, 1989); also the microinjection of a non-destructive dose of kainic acid into the intermediate part of the nucleus tractus solitarii of the rat induced hypertension (Talman et al., 1981). In a previous study we also observed hypertension accompanying the microinjection of kainic acid into the nucleus tractus solitarii of the cat (Vayssettes-Courchay et al., 1993b).

Bousquet et al. (1982) described an increase in sympathetic tone and blood pressure after injection of muscimol into the nucleus tractus solitarii of the cat; however, their method was quite different since they injected a large volume (500 nl) in only one site at the level of the obex. In our present study we used small injection volumes (50 nl) in three sites along the nucleus tractus solitarii in order to specifically reach all the baroreceptor projection sites in the nucleus tractus solitarii (Lipski et al., 1975; Donoghue et al., 1984) without reaching the adjacent areas.

It remains to be clarified why microinjections of kainic acid into the nucleus tractus solitarii abolished the cardiovascular effect of i.v. 8-OH-DPAT (Vayssettes-Courchay et al., 1993b). The main interest of kainic acid injections, frequently used in central cardiovascular research, is that this compound appears to destroy the cell bodies and not the fibers of passage. However, secondary effects of kainic acid injections have also been reported, e.g. degeneration of some axons, dendrites and glial cells, and also propagation of the excitotoxic injury in both space and time by excessive neuronal firing extending the zone of parenchymal damage away from the region of initial insult (Choi, 1991). The latter effect seems to occur in the nucleus tractus solitarii and may explain the previously obtained results (Vayssettes-Courchay et al., 1993b).

Kainic lesions of the lateral tegmental field have been reported to inhibit the baroreflex and the hypotensive, bradycardic and sympatho-inhibitory effects of 8-OH-DPAT (Clement and McCall, 1993a,b; Vayssettes-Courchay et al., 1993a). These results now become questionable in view of the present new data about the nucleus tractus solitarii. The present experiments show that the microinjection of muscimol into the lateral tegmental field induced a decrease in sympathetic nerve activity, blood pressure and heart rate followed by the disappearance of the inhibitory effect of 8-OH-DPAT. These data do not allow us to conclude whether the lateral tegmental field is more or less implicated than the rostral ventrolateral medulla because of the low sympathetic tone left after muscimol injection. They do, however, confirm the involvement of the lateral tegmental field in the central action of 8-OH-DPAT; they also confirm that this area plays a major role in the maintenance of sympathetic tone and they show that a GABAergic sympatho-inhibitory mechanism exists within the lateral tegmental field.

In conclusion, the present experiments indicate that the nucleus tractus solitarii does not appear to be an

important site for the sympatho-inhibitory effect of 8-OH-DPAT and that the lateral tegmental field appears to be a structure involved in the regulation of sympathetic tone and in the central action of 8-OH-DPAT. The data show that lesions of nervous tissue made with kainic acid are likely not to be restricted to the region in which the excitotoxic agent is microinjected and suggest caution in the interpretation of results obtained with such experiments.

References

Barman, S.M. and G.L. Gebber, 1980, Sympathetic nerve rhythm of brain stem origin, Am. J. Physiol. 239, R42.

Bennett, J.A., P.N. McWilliam and S.L. Shepheard, 1987, A γ-aminobutyric-acid-mediated inhibition of neurones in the nucleus tractus solitarius of the cat, J. Physiol. 392, 417.

Bousquet, P., J. Feldman, R. Bloch and J. Schwartz, 1982, Evidence for a neuromodulatory role of GABA at the first synapse of the baroreceptor reflex pathway; effects of GABA derivatives injected into the nucleus tractus solitarii, Naunyn-Schmied. Arch. Pharmacol. 319, 168.

Choi, D.W., 1991, Excitotoxicity, in: Excitatory Amino Acid Antagonists, Vol. 11, ed. B.S. Meldrum (Blackwell Sc. Publ.) p. 216.

Clement, M.E. and R.B. McCall, 1990, Studies on the site and mechanism of the sympatholytic action of 8-OH-DPAT, Brain Res. 525, 232.

Clement, M.E. and R.B. McCall, 1992, Evidence that the lateral tegmental field plays an important role in the central sympatho-inhibitory action of 8-OH-DPAT, Brain Res. 587, 115.

Clement, M.E. and R.B. McCall, 1993a, Lateral tegmental field involvement in the central sympatho-inhibitory action of 8-OH-DPAT, Brain Res. 612, 78.

Clement, M.E. and R.B. McCall, 1993b, Impairment of the baroreceptor reflexes following kainic acid lesions of the lateral tegmental field, Brain Res. 618, 328.

Donoghue, S., R.B. Felder, D. Jordan and K.M. Spyer, 1984, The central projections of carotid baroreceptors and chemoreceptors in the cat: a neurophysiological study, J. Physiol. 347, 397.

Gebber, G.L., J.M. Barman and M. Zviman, 1989, Sympathetic activity remains synchronized in presence of a glutamate antagonist, Am. J. Physiol. 256, R722.

Guyenet, P.G., T.M. Filtz and S.R. Donaldson, 1987, Role of excitatory amino acids in rat vagal and sympathetic baroreflexes, Brain Res. 407, 272.

King, K.A. and J.R. Holtman, 1990, Characterization of the effects of activation of ventral medullary serotonin receptor subtypes on cardiovascular activity and respiratory motor outflow to the diaphragm and larynx, J. Pharmacol. Exp. Ther. 252, 665.

King, K.A. and R.B. McCall, 1991, The effects of 8-OH-DPAT on medullary 5-HT neurons and sympathetic activity in baroreceptor denervated animals, Eur. J. Pharmacol. 200, 357.

Laubie, M., M. Drouillat, M. Dabiré, H. Cherqui and H. Schmitt, 1989, Ventrolateral medullary pressor area: site of hypotensive and sympatho-inhibitory effects of 8-OH-DPAT in anaesthetized dogs, Eur. J. Pharmacol. 160, 385.

Leone, C. and F. Gordon, 1989, Is L-glutamate a neurotransmitter of baroreceptor information in the nucleus of tractus solitarius?, J. Pharmacol. Exp. Ther. 250, 3, 953.

Lipski, J., R.M. McAllen and K.M. Spyer, 1975, The sinus nerve and baroreceptor input to the medulla of the cat, J. Physiol. 251, 61.

Mandal, A.K., J. Kellar and R.A. Gillis, 1991, The subretrofacial nucleus: a major site of action for the cardiovascular effects of 5-HT_{1A} and 5-HT_2 agonist drugs, in: Serotonin: Molecular Biology, Receptors and Functional Effects, eds. J.R. Fozard and R.P. Saxena (Birkhäuser Verlag) p 289.

McCall, R.B., B.N. Patel and L.T. Harris, 1987, Effects of serotonin 1 and serotonin 2 receptor agonists and antagonists on blood pressure, heart rate and sympathetic nerve activity, J. Pharmacol. Exp. Ther. 242, 1152.

McCall, R.B., M.E. Clement and L.T. Harris, 1989, Studies on the mechanism of the sympatholytic effect of 8-OH-DPAT: lack of correlation between inhibition of serotonin neuronal firing and sympathetic activity, Brain Res. 501, 73.

Middlemiss, D.N. and Fozard, J.R., 1983, 8-hydroxy-2(di-*n*-propylamino)tetralin discriminates between subtypes of the 5-HT recognition site, Eur. J. Pharmacol. 90, 151.

Nosjean, A. and P.G. Guyenet, 1991, Role of the ventrolateral medulla in the sympatholytic effect of 8-OH-DPAT in rats, Am. J. Physiol. 260, R600.

Ramage, A.G. and J.R. Fozard, 1987, Evidence that the putative 5-HT_{1A} receptor agonists 8-OH-DPAT and ipsapirone have a central hypotensive action that differs from that of clonidine in anaesthetized cats, Eur. J. Pharmacol. 138, 179.

Talman, W.T., 1989, Kynurenic acid microinjected into the nucleus tractus solitarius of rat blocks the arterial baroreflex but not responses to glutamate, Neurosci. Lett. 102, 247.

Talman, W.T., M.H. Perrone and D.J. Reis, 1981, Acute hypertension after local injection of kainic acid into the nucleus tractus solitarii in rats, Circ. Res. 48, 292.

Vayssettes-Courchay, C., F. Bouysset, T.J. Verbeuren and M. Laubie, 1993a, Role of the lateral tegmental field in the central sympatho-inhibitory effect of 8-OH-DPAT in the cat, Eur. J. Pharmacol. 236, 121.

Vayssettes-Courchay, C., F. Bouysset, T.J. Verbeuren and M. Laubie, 1993b, Role of the nucleus tractus solitarii and the rostral depressive area in the sympatholytic effect of 8-hydroxy-2-(di-*n*-propylamino)tetralin in the cat, Eur. J. Pharmacol. 242, 37.

Verberne, A.J.M. and P.G. Guyenet, 1992, Medullary pathway of the Bezold-Jarisch reflex in the rat, Am. J. Physiol. 263, R1195.

Wang, W.H. and T.A. Lovick, 1992, Excitatory 5-HT_2 mediated effects on rostral ventrolateral medullary neurones in rats, Neurosci. Lett. 141, 89.