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BRIEF COMMUNICATION

Effect of 6-OHDA Injected Into the Locus Coeruleus on Apomorphine-Induced Aggression[1]

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PUCIŁOWSKI, O , W KOZAK AND L VALZELLI *Effect of 6-OHDA injected into the locus coeruleus on apomorphine-induced aggression* PHARMACOL BIOCHEM BEHAV 24(3)773–775, 1986 —Bilateral microinjections of 6-hydroxydopamine (6-OHDA) into the nuclei loci coerulei (LC) of male Wistar rats resulted in significant depletion of mesencephalic and striatal norepinephrine, accompanied by a small reduction in dopamine content only in the striatum Apomorphine (2 5 mg/kg IP) induced marked aggression consisting of prolonged posturing, vocalization and attacks only in 6-OHDA lesioned animals Biochemical analysis revealed that 6-OHDA antagonized the ability of apomorphine to raise the serotonin concentration in the striatum It is concluded that the LC neurons play an inhibitory role in apomorphine-induced aggressiveness and the involvement of serotonergic neurons is suggested

Aggressive behavior Apomorphine Locus coeruleus Norepinephrine 6-Hydroxydopamine Rat

IT has been suggested that apomorphine (APO)-induced aggression involves a modulatory noradrenergic component Clonidine (CLO) treatment increases this kind of induced aggressiveness [2, 3, 10, 11], and a similar potentiation was observed after electrolytic lesion of the nuclei loci coerulei [5], the main area containing noradrenergic cell bodies giving ascending projections to the cortex and hippocampal areas [6] Since clonidine inhibits noradrenaline release from noradrenergic neurons, due to the stimulation of presynaptic alpha-2 adrenoceptors [12] and reduces the bioelectrical activity of the locus coeruleus cells [1], the drug might exert its aggression-potentiating effect through the locus coeruleus system In order to obtain further information about the involvement of the locus coeruleus in APO-induced aggression, we studied the effect of APO in rats with chemical (6-hydroxydopamine) lesions of the locus coeruleus

METHOD

Male Wistar rats (Charles River, Italy) weighing 250± 10 g were housed four per cage (transparent Macrolon cages 42×26×15 cm) with free access to standard laboratory chow and tap water in controlled laboratory conditions with a 12 12 hr light/dark cycle (lights on at 8 00 hr) 6-Hydroxydopamine was injected stereotaxically according to Pellegrino *et al* [9] into the loci coerulei (5 μg in 1 0 μl on each side, at a rate of 1 μl/min, controls received an equal volume of solvent, 0 2 percent ascorbic acid in distilled water) using the coordinates P 1 6 mm, L±1 0 mm, H−3 0 mm and an SGE microsyringe, by means of a Stoelting stereotaxic apparatus Ten days were allowed for postsurgical recovery

For aggression test rats were paired lesioned-lesioned or control-control and injected IP with 2 5 mg/kg of APO, the dose previously found to be subthreshold for inducing aggression Ten min after APO administration, paired rats were scored over 25 min in a Plexiglas arena (22×17×24 cm) for (a) the total time spent in aggressive boxing postures, (b) the number of vocalizations and (c) the number of biting attacks Only pairs with both animals properly lesioned (biochemically verified) were analysed statistically Biochemical analysis was performed on separate groups of animals, lesioned and controls Control animals received the solvent and APO-treated rats were injected IP 10 min before decapitation in order to evaluate the drug's effect on brain amines (norepinephrine, dopamine, serotonin) and 5-hydroxyindolacetic acid concentrations The details of the procedure, including the high performance liquid chromatog-

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TABLE 1

BRAIN AMINE AND METABOLITE 5-HYDROXYINDOLACETIC ACID CONCENTRATIONS BEFORE AND AFTER APOMORPHINE (APO) TREATMENT IN CONTROL AND 6-OHDA-LESIONED RATS (LC)

Groups	No of rats	Brain concentrations (ng/g ± SE) NE	DA	5-HT	5-HIAA
Striatum					
Control	6	296 ± 31	9230 ± 270	482 ± 16	496 ± 30
LC-lesioned	5	100 ± 16‡	8350 ± 210*	523 ± 22	442 ± 21
Control +APO	6	284 ± 55	9150 ± 160	593 ± 37§	559 ± 31
LC-lesioned+APO	6	87 ± 20‡	8200 ± 300*	519 ± 39	408 ± 29†
Mesencephalon					
Control	6	322 ± 19	94 ± 7	575 ± 29	524 ± 23
LC-lesioned	6	158 ± 14‡	104 ± 21	558 ± 12	478 ± 10
Control +APO	6	288 ± 18	95 ± 4	521 ± 25	525 ± 16
LC-lesioned+APO	6	164 ± 7‡	110 ± 9	549 ± 9	490 ± 18

*=$p<0.05$ vs respective controls
†=$p<0.01$ vs respective controls
‡=$p<0.001$ vs respective controls
§=$p<0.05$ vs control not treated with APO

raphy with electrochemical detection (HPLC-EC), were described elsewhere [8,13] Statistical evaluation of the results was made using the Student's t-test for the biochemical data, and the Mann-Whitney U-test for behavioral measures

RESULTS

Rats with bilateral lesions of the LC showed significant ($p<0.001$) depletion of NE in the striatum (by 66%) and mesencephalon (51%), accompanied by a small (10%) but significant decrease in striatal DA The APO-treatment raised both striatal 5-HT (23%) and 5-HIAA (13%) in control rats, though only the former reached statistical significance ($t=2.74$, $p<0.05$) 6-OHDA-treated animals did not present any significant serotonergic change after APO injection (Table 1)

No signs of spontaneous aggression among the grouped animals were observed APO elicited a marked aggressive behavior only in pairs of lesioned rats (Fig 1)

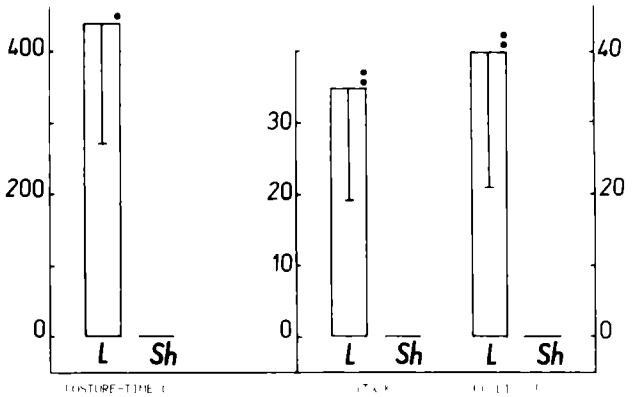

FIG 1 Effect of LC lesions on apomorphine-induced aggression in paired rats during 25 min of observation L=lesioned (14 animals, 7 pairs) Sh=sham lesioned (14 animals, 7 pairs) ●=$p<0.05$ ●●=$p<0.01$

DISCUSSION

The data obtained indicate that 6-OHDA-induced destruction of noradrenergic neurons in the LC enhances the aggression elicited by APO administered in amount usually ineffective to induce aggression in normal rats In contrast to control rats, lesioned animals displayed a marked aggressiveness following the subthreshold dose of 2 5 mg/kg of APO This finding is in line with previous data provided by electrolytic lesioning method [5] and supports the hypothesis that the dorsal noradrenergic bundle plays an inhibitory role in effective aggression induced by APO [5,10] Furthermore, LC lesion prevented the biochemical changes typically produced by APO, i e , the rise in both 5-HT and 5-HIAA concentrations [3,7] The relatively slight increase in 5-HIAA concentrations observed in control rats treated with APO was probably due to the low dose of APO used Clonidine has been reported to similarly potentiate the behavioral effects of APO and to reduce the parallel rise of the brain 5-HIAA [2, 3, 10] 6-OHDA lesions performed in the present study, apparently are not specific for NE neurons of LC, since there is a drop in striatal dopamine However, it is not clear at present whether this minor change in dopamine level depends on a direct effect of the neurotoxin on dopaminergic neurons or on a new equilibrium within interacting monoaminergic networks Signs of dopaminergic supersensitivity have been reported in rats following the electrolytic lesions of the locus coeruleus [4] The data obtained seem to confirm that the inhibition of noradrenergic transmission impairs serotonin release by neurons normally activated by APO [3,7], also indicating the presence of an interaction between noradrenergic and dopaminergic neurons in the brain

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REFERENCES

1 Cederbaum, J M and G K Aghajanian. Catecholamine receptors on locus coeruleus neurons Pharmacological characterization *Eur J Pharmaco* **44**, 375–385, 1977
2 Gianutsos, G , M D Hynes and H Lal Enhancement of morphine-withdrawal and apomorphine-induced aggression by clonidine *Psychopharmacol Commun* **2**: 165–171, 1976
3 Hahn, R A , M D Hynes and R W Fuller Apomorphine-induced aggression in rats chronically treated with oral clonidine modulation by central serotonergic mechanisms *J Pharmacol Exp Ther* **220** 389–393, 1982
4 Kostowski, W In *Receptors and Drug Action*, edited by W B Essman New York Plenum Press, 1980, pp 45–67
5 Kostowski, W , A Czlonkowski, M Jerlicz, A Bidzinski and M Hauptmann Effect of lesions of the locus coeruleus on aggressive behavior in rats *Physiol Behav* **21**· 695–699, 1978
6 Lindvall, O and A Bjorklund Organization of catecholamine neurons in the rat central nervous system In *Handbook of Psychopharmacology*, vol 9, edited by L L Iversen, S D Iversen and S H Snyder New York Plenum Press, 1978, pp 139–222
7 Maj, J Dopaminergic drug effects upon serotonin neurons In *Current Developments in Psychopharmacology*, vol 3, edited by W B Essman and L Valzelli, New York Spectrum, 1976, pp 55–83
8 Mefford, I N and J D Barchas Determination of tryptophan and metabolites in rat brain and pineal tissue by reversed-phase high-performance liquid chromatography with electrochemical detection *J Chromatogr* **181**· 187–193, 1980
9 Pellegrino, L J , A S Pellegrino and A J Cushman *A Stereotaxic Atlas of the Rat Brain* New York Plenum Press, 1979
10 Puciłowski, O , W Kozak, L Valzelli and S Garattini Modification of apomorphine-induced fighting in rats after chronic oral treatment with drugs altering noradrenergic transmission *Eur J Pharmacol*, in press
11 Senault, B Amines cerebrales et comportement d-agressivité intra-specifique induit par l'apomorphine chez le rat *Psychopharmacologia* **34**: 143–154, 1974
12 Starke, K Regulation of noradrenaline release by presynaptic receptor systems *Rev Physiol Biochem Pharmacol* **77**· 1–124, 1977
13 Valzelli, L and S Garattini Biogenic amines in discrete brain areas after treatment with monoamineoxidase inhibitor *J Neurochem* **15**· 259–261, 1968