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Norepinephrine-Mediated Suppression of Apomorphine-Induced Aggression and Locomotor Activity in the Rat Amygdala

OLGIERD PUCILOWSKI, EWA TRZASKOWSKA, WOJCIECH KOSTOWSKI AND LUIGI VALZELLI*

*Department of Pharmacology and Physiology of the Nervous System, Psychoneurological Institute Al. Sobieskiego 1-9, PL-02957 Warszawa, Poland and *Mario Negri Institute for Pharmacological Research, Via Eritrea 62, 20157, Italy*

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PUCILOWSKI, O., E. TRZASKOWSKA, W. KOSTOWSKI AND L. VALZELLI. *Norepinephrine-mediated suppression of apomorphine-induced aggression and locomotor activity in the rat amygdala.* PHARMACOL BIOCHEM BEHAV **26**(2) 217–222, 1987.—The effect of injections of norepinephrine (NE)-depleting toxin DSP-4 into the central amygdala (AMY) on apomorphine-induced fighting (AIF) was studied. In addition, the influence of such treatment on related parameters such as spontaneous activity, pain sensitivity and changes in locomotion after (+)3-PPP or apomorphine (1 mg/kg SC each) were verified. Finally, injections of NE or phenylephrine into the AMY five min before AIF were performed. DSP-4 induced marked (−71%) and selective fall in NE within the AMY accompanied by significant increase in aggressive response to 5 mg/kg of apomorphine. DSP-4-treated animals were less active in the open field and more sensitive to pain in a hot plate test. They were also more responsive to locomotor-augmenting action of apomorphine. Significant suppression of AIF was seen after injections of NE and phenylephrine into the AMY. The results suggest that NE input to the AMY plays an inhibitory role in dopamine-related locomotion and aggressivity. Moreover, amygdalar NE appears to be involved in general activity and pain perception modulation.

Norepinephrine Amygdala Affective aggression Apomorphine Locomotor activity
N-[2-chloroethyl]-N-ethyl-2-bromobenzylamine (DSP-4) Rat

CENTRAL noradrenergic neurons are thought to exert an inhibitory control over affective aggression. The notion has been based upon the observation of enhanced aggressiveness, isolation-induced in mice and shock-induced in rats, after administration of the catecholamine depleting neurotoxin 6-hydroxydopamine (6-OHDA) [5, 25, 35]. However, some negative or contradictory data have been published as well [3,6]. Pharmacological manipulation of noradrenergic transmission has also brought conflicting results (cf. [33]). These discrepancies have become clearer ever since Geyer and Segal demonstrated the opposite effects on shock-induced fighting (SIF) of norepinephrine (NE) and dopamine (DA) when administered into the brain ventricles: the former produced inhibition while the latter brought about facilitation [9]. Both 6-OHDA, if given without suitable premedication, and many other pharmacological agents used in studies of aggressive behavior were known to influence NE and DA neuron function in parallel. Moreover, it was soon demonstrated that functional differences existed between ascending NE pathways. The dorsal bundle originating in the nuclei loci coerulei (LC) played an inhibitory role [16], while the ventral bundle seemed to facilitate affective aggression [17].

At present considerable evidence has been collected of noradrenergic LC-mediated inhibitory control over affective as well as predatory aggression [8, 16, 22, 28, 29, 34]. This negative influence can be realized at different limbic structures known to participate in aggressive behavior modulation, which are innervated by NE-containing neurons from the LC. We have previously demonstrated that the nucleus accumbens septi might be one of the likely sites of such NE action [30]. In the present study we have decided to concentrate on the amygdala (AMY). The structure receives most NE input from the LC [7], its importance for expression of affective aggression is well documented [14, 21, 32], and amygdalar NE has already been implicated in control of the rat predatory behavior, which constitutes a separate class of aggression [18,34]. AMY also contains high concentration of DA, whose facilitatory role in affective fighting is supported by firm evidence (cf. [27]). For selective destruction of NE-containing neurons within the AMY we used direct microinjections of noradrenergic neurotoxin N-[2-chloroethyl]-N-ethyl-2-bromobezylamine (DSP-4), and affective aggression was studied in the apomorphine-induced fighting (AIF) paradigm. Similar in behavioral characteristics to other non-pharmacological models of affective aggression AIF offers a more direct approach to the problem of NE-DA interaction, since apomorphine acts as a direct postsynaptic DA receptor agonist. The possibility of amygdalar NE modulation of DA transmission was further assessed in the locomotor activity test: hypolocomotion was induced by SC administration of the DA autoreceptor agonist (+)-3-

TABLE 1

THE EFFECT OF DSP-4 INJECTION INTO THE AMY ON BIOGENIC AMINE AND METABOLITE CONCENTRATIONS (MEAN VALUES OF 5 DETERMINATIONS IN ng/g ± SE)

	NE	DA	DOPAC	HVA	5-HT	5-HIAA
Control	185 ± 38	1622 ± 110	296 ± 16	128 ± 8	567 ± 21	336 ± 19
DSP-4	54 ± 13*	1431 ± 184	206 ± 39	125 ± 17	514 ± 11	301 ± 13

*=$p<0.01$ vs. control, t-test.

[3-hydroxyphenyl]-N-n-propylpiperidine, (+)3-PPP, and a low dose of apomorphine (APO) was used to elicit hyperactivity. In addition, we determined the effect of intra-amygdalar DSP-4 on spontaneous behavior in the open field and on the reactivity to noxious stimuli in the hot plate test. In a separate experiment we checked the effect of inverse manipulation with NE in the AMY on AIF, i.e., we microinjected NE and alpha-adrenoceptor agonist l-phenylephrine solutions into the structure prior to the aggression test.

METHOD

Animals

Male Wistar rats weighing 200–220 g were housed four per cage under standard laboratory conditions with free access to chow and water. For AIF testing the animals were screened for their responsiveness to APO. Rats were injected IP with 10 mg/kg of APO HCl (Sandoz, Switzerland) and observed in groups of three for 5 min or until the first symptoms of aggression appeared. The aggressive ones were then moved to individual cages to be aggregated again after the drug action had subsided. On this basis the animals were divided into high- and low-aggressive (no fighting during 5 min) rats.

Neurotoxin Injections

As the intracerebral injections of DSP-4 were found also to deplete serotonin (5-HT) concentration [30], to prevent that, all animals, including controls, were pretreated 45 min before surgery with the 5-HT uptake inhibitor citalopram HBr (Lundbeck, Denmark) 10 mg/kg IP. The animals anesthetized with ethyl ether were fixed in a Stoelting stereotaxic instrument with the incisors base 5 mm above the interaural line. The 30-gauge injection cannula connected via polyethylene tubing to a 10 μl S.G.E. syringe was positioned in the central AMY according to the following coordinates: A 5.4 mm, L ±4.5 mm, H 2.5 mm above the interaural line [23]. The rats were injected with a freshly prepared aqueous solution of DSP-4 (Astra, Sweden), 12 μg in 2 μl on each side at a rate of 1 μl per min. Relatively large volume was used in order to ensure penetration of the toxin to various parts of the AMY, thereby the most thorough lesion of NE-containing terminals within the structure. Control, sham-operated animals received an equal volume of redistilled water. Seven days were allowed for postoperative recovery.

Behavioral Protocol

In one group of DSP-4 and control rats a series of behavioral tests was commenced with a three-day interval between each successive test. At the beginning the animals were tested in the open field, then subjected to pain sensitivity measurement in the hot plate test, and finally the influence of DSP-4 on locomotor activity elicited by DA receptor agonists was checked.

Open Field

The open field was a rectangular arena 60×60 cm, its floor being divided into 16 squares. Each rat was placed in the arena for 5 min and the total number of square crossings, the number of rearings, and immobility score (5 sec=1 score point) were noted.

Hot Plate Test

Each rat subjected to this test was placed in a hot plate device (HP-1, COTM, Poland) adjusted to a temperature of 57°C. The latency of kick response or licking of the paws in seconds was recorded in a single trial.

Locomotor Activity

Automatic recording of locomotor activity was done in an activity meter (UMA-2, COTM, Poland) operating on the same principle as the Animex instrument. The animals from DSP-4 and water-injected groups were administered SC either saline, 1 ml/kg, (+)3-PPP (Astra, Sweden) or APO, 1 mg/kg per ml each. After 5 min each rat was placed in an activity meter and the numbers of horizontal and vertical movements were recorded separately over 10 min period.

AIF Test

In another group of rats pretested for aggressive response to APO DSP-4 lesions of the AMY were made. AIF was performed seven to ten days after surgery separately in high-and low-aggressive groups. Pairs of identically treated (DSP-4-DSP-4 or water-water) rats were injected IP with 5.0 mg/kg of APO (low-aggressive rats were additionally treated with 20 mg/kg of APO 4 days later). Immediately thereafter they were placed in a transparent plastic observation arena (30×15×40 cm). The following items were scored for each pair over a 20 min observation period: the total time spent in aggressive boxing stance, the number of audible vocalizations and the number of biting attacks.

Biochemical Determinations

The efficacy of chemical destruction of noradrenergic innervation in the AMY was verified biochemically in a separate group of DSP-4 and vehicle-treated rats. Seven days after surgery the animals were decapitated, their brains removed, block of tissue containing the AMY and fragments of the cortex was dissected on dry ice and stored at −30°C until

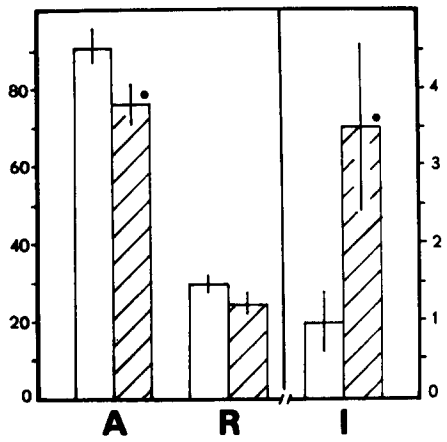

FIG. 1. Effect of DSP-4 injections into the AMY on behavior in the open field. Open bars—control animals (n=12), hatched bars—DSP-4-treated animals (n=12). A=locomotor activity, R=rearings, I=immobility score. ●=$p<0.05$ vs. control, t-test.

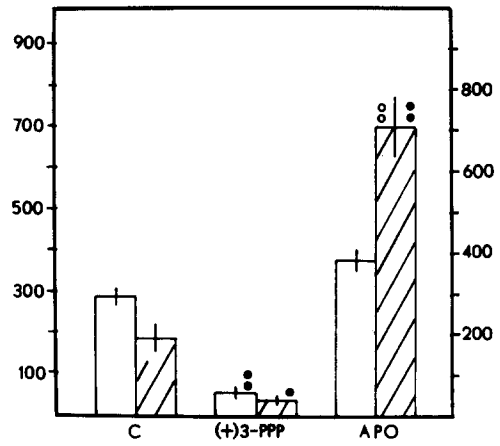

FIG. 2. Effect of DSP-4 injections into the AMY on locomotor activity (horizontal movements) induced by DA receptor agonists. C=control treatment (saline), ●=$p<0.05$, ●●=$p<0.01$ vs. C, ○○=$p<0.01$ vs. water-injected controls (open bars), Duncan test. Seven rats per group.

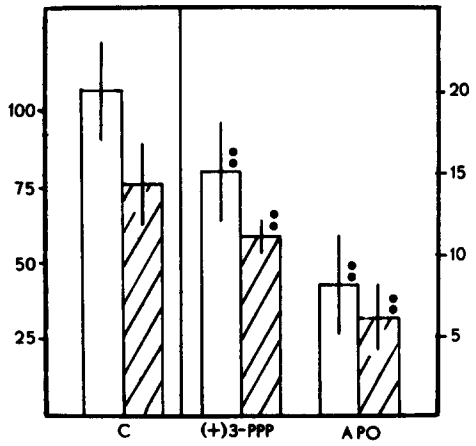

FIG. 3. Effect of DSP-4 injections into the AMY on rearing induced by DA receptor agonists. For details see Fig. 2.

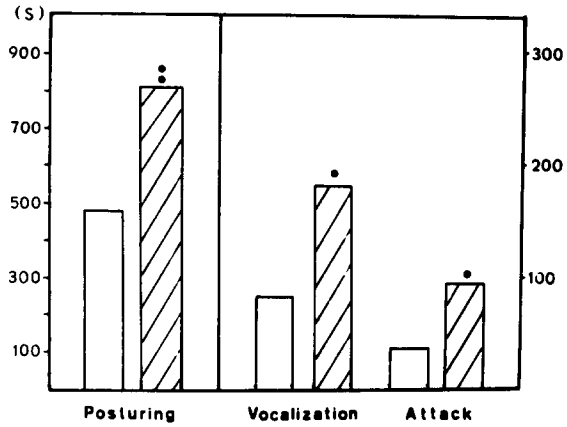

FIG. 4. Effect of DSP-4 injections into the AMY on AIF in high-aggressive rats. Median values from seven pairs of rats per group. ●=$p<0.05$, ●●=$p<0.02$ vs. water-injected controls (open bars), Mann-Whitney test.

analysis (2–4 days later) [10]. The concentrations of NE, DA, 5-HT as well as 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in the amygdalar tissue were measured using HPLC with electrochemical detection. The apparatus and modifications to the original method of Mefford and Barchas [20] were described previously [30].

Cannula Implantation

Under ethyl ether anesthesia high-aggressive animals were implanted sockets containing two parallel stainless steel guide cannulas (22-gauge) spaced 9.0 mm apart, aimed 2.0 mm above the final injection site. The coordinates for injection were the same as those used for DSP-4 lesions of the AMY. The socket was fixed to the skull with three metal screws and acrylic cement, and a stainless steel mandrel was placed in each cannula between injection sessions. After surgery animals were housed singly in wire mesh cages and behavioral testing was started seven days later.

Injection Procedure

Injections were given to hand-held animals which had been handled for 3 days prior to the first injection session. NE bitartarate (Koch-Light, U.K.) or l-phenylephrine HCl (Sigma, U.S.) were dissolved in redistilled water and 0.5 μl containing 20 μg of the drug was injected on each side via a 30-gauge cannula connected by polyethylene tubing to a Hamilton syringe. The tip of injection cannula was extending 2.0 mm below the bottom of the guide cannula. The injection rate was 1 μl/min, with the cannula left in place for additional 30 sec. Implanted rats were randomly divided into two equal groups. One was injected with NE while the other was ad-

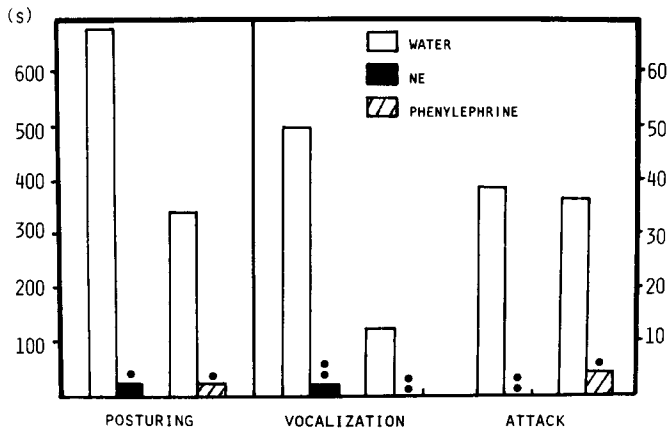

FIG. 5. Effect of NE and phenylephrine injected into the AMY on AIF. Median values from seven pairs of rats per group. ●=$p<0.05$, ●●=$p<0.02$ vs. water-injected controls, Wilcoxon test.

ministered the vehicle. Five min after injection of the drug to a pair of rats the AIF test was commenced as described previously. After one week the injection session was repeated but this time water-injected group received NE and previously NE-treated rats were given water. Phenylephrine was given accordingly, so that each animal received only two microinjections, water and the drug. After completing the behavioral testing the animals were sacrificed, their brains removed and the cannula placement verified on frozen-cut sections. Only pairs of rats with both animals properly implanted were analysed by a Wilcoxon matched-pair test, two tailed.

The statistical significance of the data from AIF in DSP-4 experiment was determined by the two tailed Mann-Whitney U test. In both experiments with AIF group statistics are represented by median values, because of a nonuniform distribution of the experimental data. Biochemical results and the data from the open field and hot plate tests were analysed by the two tailed Student's *t*-test for independent measures, and 2×3 ANOVA followed by Duncan multiple range test was used to determine the statistical significance of DSP-4 on locomotor activity after DA receptor stimulants. In all these tests the data are presented as mean±standard error of the mean. Probability level of $p=0.05$ was chosen as the significance limit in all tests.

RESULTS

Bilateral injections of DSP-4 into the AMY (plus citalopram) induced a 71% decrease in NE which was significant at $p<0.01$. Other amine and metabolite concentrations did not change significantly although 5-HT and DOPAC showed a tendency to decrease (Table 1).

The DSP-4-treated rats were less active in the open field, their score of motility was lower and immobility period longer than that of controls (Fig. 1). They were also more sensitive to a noxious thermal stimulus in the hot plate test. Latency in sec of kick/lick response was significantly shorter in this group (n=16), mean=8±1, as compared to water-injected controls (n=16), mean=11±1 ($t=2.406$, $p<0.05$).

Further differences between both groups were found in locomotor activity elicited by the DA receptor agonists. For horizontal movements 2×3 ANOVA revealed a significant effect of the lesion, $F(1,36)=5.6$, $p<0.025$, drug treatment, $F(2,36)=95.7$, $p<0.001$, as well as the lesion × treatment interaction, $F(4,36)=18.7$, $p<0.001$. Multiple comparisons with the Duncan test showed that stimulation of DA autoreceptors with (+)3-PPP suppressed to a similar extent motility in both groups. However, hyperactivity after APO was significantly more pronounced in the DSP-4 group (Fig. 2). Vertical movements (rearings) were suppressed by both drugs, treatment effect, $F(2,36)=49.3$, $p<0.001$, while neither lesion effect, $F(1,36)=1.8$, nor interaction lesion × treatment, $F(4,36)=1.0$, were found significant (Fig. 3).

In high-aggressive rats DSP-4 injected into the central AMY significantly augmented all aggressive behavior parameters (Fig. 4). However, in low-aggressive sample neither 5 nor 20 mg/kg of APO was able to elicit fighting in both the DSP-4 and vehicle-injected animals. Direct bilateral microinjections of NE or l-phenylephrine into the AMY potently suppressed AIF (Fig. 5).

DISCUSSION

The present data indicate that the amygdalar NE transmission exerts an inhibitory control over affective aggression induced by APO. This is in line with a number of studies in which chemically-induced NE depletion in the brain was found to potentiate affective fighting in various models [5, 8, 22, 30, 35]. This negative influence of NE mechanisms on affective aggression has been attributed to the ascending LC projection, as destruction of NE-containing neurons in this site reportedly enhanced fighting [8, 11, 28]. Furthermore, peripherally administered DSP-4 was also found to augment SIF [22], and the toxin is known to affect primarily NE neurons of the LC origin [12]. The effects of NE and phenylephrine microinjection corroborate the above results. Intraventricular injections of the amine were shown to decrease SIF [1,9]. Interestingly, microinjections into the medial AMY were also found to suppress muricidal behavior, a distinct class of aggression by behavioral and neurochemical criteria [34,36]. Thus inhibitory action of amygdalar NE, mediated via alpha-adrenoceptors, is neither class- nor model-specific, and possibly it is realized through modulation of some processes equally vital to both affective and predatory aggression.

Spontaneous open field activity after intraamygdalar DSP-4 was significantly lower than that of controls. Similar results were reached with electrolytic lesions of the LC [15] or peripheral DSP-4 administration [4]. Hypersensitivity to noxious stimuli after inhibition of NE transmission within the AMY corresponds with earlier data from this laboratory ([24], but see also [31]).

The main aim of our study was to verify the hypothesis that NE innervation of the AMY, originated in the LC, can negatively influence DA-mediated affective aggression. In the model used here fighting is elicited due to massive stimulation of postsynaptic DA receptors, presumably the most important being those within the terminal areas of the mesolimbic system, e.g., in the nucleus accumbens septi [27]. Another behavioral phenomenon ascribed to postsynaptic DA receptor stimulation in the nucleus accumbens is locomotor activity. Here, APO-induced hyperlocomotion was used as a model of postsynaptic DA receptor activation, and this effect of the drug was also significantly enhanced by DSP-4 treatment. Hypolocomotion after (+)3-PPP, reportedly an effect of DA autoreceptor stimulation [2], was not altered by DSP-4, suggesting that only the

postsynaptic DA component is modulated by NE amygdalar input. Thus, since both locomotor activity and affective aggression appear to be closely related to DA mesolimbic neuron function DSP-4-induced changes in spontaneous and APO-elicited behavior might be explained by shift in mesolimbic DA neuron function. Apparently some degree of supersensitivity develops in the postsynaptic DA receptors involved in both behavioral phenomena as a consequence of NE depletion in the AMY. The nature of interaction between the amygdalar NE and the mesolimbic DA awaits resolving. DA mesolimbic neurons also terminate within the AMY [7]. Moreover, there are both direct and indirect connections between the AMY and the nucleus accumbens [13,26]. However, the neurochemical nature of these connections remains to be clarified. Possibly NE input from the LC to the AMY acts to inhibit DA activity in the nucleus accumbens indirectly. Within the AMY NE and DA-containing neurons are located in the vicinity of each other [7]. By cancelling or diminishing such negative, NE-mediated control over the mesolimbic DA transmission DSP-4 is able to enhance AIF and APO-induced locomotion. This tentative explanation finds some support in the biochemical evidence. 6-OHDA-induced lesion of the LC was found to raise cortical levels of the DA and its acid metabolites suggesting inhibitory influence of LC NE on DA transmission [11]. Using in vivo voltammetry Louilet and co-workers have recently demonstrated that DA agonists injected into the AMY can suppress DA neuron activity in the nucleus accumbens [19]. Accordingly, a functional link between NE LC-AMY projection and DA mesolimbic neurons in the nucleus accumbens may also be dopaminergic. Interestingly, microinjections of DA into the cortico-medial AMY resulted in facilitation of SIF, apparently secondary to changes in pain sensitivity. Bilateral injections of either alpha or beta adrenoceptor antagonists failed to alter fighting [31]. However, prolonged NE depletion due to toxin action can obviously induce some adaptive changes within the AMY neurons which do not develop after single injection of adrenergic antagonists. These processes, apart from presumed DA involvement, may also include changes in activity of other transmitters localized in the AMY and of known importance for aggressive behavior control, such as 5-HT, acetylcholine or gamma-aminobutyric acid. Finally, yet another conclusion may be drawn from the present data, that amygdalar NE mechanisms do not seem to be critically involved in resistance to aggression-promoting action of APO in a subpopulation of experimental animals.

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