MONOAMINERGIC CONTROL OF AFFECTIVE AGGRESSION

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Abstract. The aim of the present study is to present the experimental evidence, mainly that collected over recent years by the author, in support of the involvement of the dopaminergic mesolimbic system in the mechanism of affective aggression in the rat and its interactions with other monoaminergic systems. Dopamine has been found to play an important facilitatory role in affective aggression, accomplished, at least in its essential part by the mesolimbic A10 neurons projecting into the nucleus accumbens septi (NAS). Norepinephrine inhibits this behavior, the effect being mediated by the locus coeruleus ascending neurons reaching NAS and the amygdala (AMY), and involving activation of $\alpha_1$ adrenoceptors. Also serotonergic effects on affective aggression are of inhibitory nature. They are conveyed by the neurons of the dorsal raphe, but not of the median raphe, projecting into the AMY. The NAS does not play any important part in the serotonergic control of aggression. There appears to exist a reciprocal interaction between these three monoaminergic systems in respect to their modulatory function in affective aggression. The significance of these findings for diagnosis, treatment and prevention of violent behavior in the clinic is discussed.

INTRODUCTION

Central monoaminergic neurons appear to play an essential role in the control of affective aggression. Notwithstanding the considerable evidence provided by pharmacological studies with systemically admini-
stered drugs or toxins only a few papers have been devoted to the problem of involvement of particular monoaminergic pathways in the modulation of affective aggression. To fill this gap a series of experiments was performed which investigated the effects of chemical destruction of monoaminergic neurons as well as systemic and intrastructural drug injections on affective aggression.

Exaggerated aggressiveness or violence might be a symptom of organic disease or a result of action of different external factors, e.g. environmental influences. From the clinical standpoint it is essential to distinguish healthy, aggressive subjects, whose violent behavior has a politico-economic and cultural background and, as such, has no parallels in the animal world, from aggressive patients whose behavioral pathology has its origins in the malfunctioning control exercised by the nervous system (138). Pathological aggression is a symptom observed in various diseases of the central nervous system such as epilepsy, organic brain syndrome, Gilles de la Tourette's syndrome, Down's syndrome, Lesch-Nyhan syndrome or tumors of the CNS, particularly those localized in the septum, hypothalamus or limbic structures. It frequently accompanies behavioral syndromes of not established organic background like psychoses, personality disorders, neuroses and affective disorders. Aggression occurs during drug abuse (morphine, amphetamine, LSD, cocaine, cannabis, and alcohol), especially when environmental factors are superimposed on drug-induced pathology, e.g. violent behavior in narcotic abstinent addicts. Aggressive behavior has been described in various diseases such as phenylketonuria, hepatic encephalopathy, allergy, lead poisoning or herpes simplex viral infection. Aggression is also associated with some endocrine disorders such as hyperthyroidism, Cushing's syndrome, hypoglycemia or disturbed parathyroid function (18, 19, 30, 41, 45, 47, 75, 104, 128, 131).

Neither causes of pathological aggressiveness nor central mechanisms responsible for manifestations of aggressive behavior are clear. In biological research into aggression the most promising hypothesis has linked aggressive reactions with dysfunction in the central monoaminergic mechanisms controlling behavior. The three monoamines, norepinephrine (NE), dopamine (DA) and serotonin (5-HT) essential for the function of the CNS, appear to play a vital role in the control of aggressive behavior (29, 99). The present review is devoted to the description of the role played by each monoamine and their interactions in relation to the modulation of affective aggression. It has been aimed especially at providing an account of the author's contribution to the experimental analysis of the causes of this category of aggression.
AFFECTIVE AGGRESSION

There are different forms of aggressive behavior which depend on the triggering factors, on social context (isolated vs. grouped objects) or individual genetic predisposition (62, 129). Neurobiology distinguishes two main classes of aggression, defense and offense (1, 3, 99), which appear to be differently organized in the brain (33). This classification appears particularly suitable for investigation of the neural and neurochemical mechanisms of aggression. It should be understood, however, that since aggression has long been recognized as a complex behavior involving many motivational and behavioral components (129), various classifications of this behavior can be employed depending on the problem under investigation. One of the earlier schemes proposed by Moyer distinguished 8 categories of aggression on the basis of eliciting stimulus (inter-male, fear-induced, irritable, predatory, maternal, sex-related, territorial, instrumental) (83). Recently, as the ethological approach became more popular, a new classification has been proposed by Brain (14). He defined 5 classes of aggression basing on the utility of the behavior to the animal: self-defensive, parental, predatory, social and reproduction termination. This subdivision, although more closely describing the behavior in its natural setting does not seem, according to the present author, to provide any advantage when the brain mechanisms of aggression are investigated. It appears superior instead in studies of the effects of various drugs or environmental manipulations on aggression. This report deals with defensive aggression in rats characterized by Reis as the behavior consisting of typical defensive upright or sideways posture. It is accompanied by vocalization and various symptoms of activation of the sympathetic nervous system such as accelerated heart rate, increased blood pressure or piloerection (99). This type of aggression, also termed affective behavior, can be elicited in the laboratory by different methods. In psychopharmacology the most popular are the shock-induced fighting (SIF) and apomorphine-induced fighting (AIF) models (11, 13, 26, 30, 73). In the latter aggression is elicited by administration of apomorphine (APO), a direct dopaminergic receptor agonist (76, 106). The doses used are rather high, usually over 5 mg/kg, and the effect, i.e. aggression, is ascribed to the stimulation of postsynaptic receptors (40). Behaviorally it resembles the SIF model, although usually fighting is more intense, it is accompanied by symptoms of hyperreactivity and the behavior appears to possess a compulsory character. The rats once involved in a combat, stay in aggressive posture for long periods or otherwise frequently assume aggressive stance. Biting attack,
directed at a snout, is another typical feature of this model of aggression. Given these differences, AIF has been sometimes termed irritable aggression, though not being excluded from broader category of affective aggression (11). AIF can be elicited only in a subpopulation of responsive animals; adult male rats of some strains e.g. Wistar rats are thus much more likely to react with aggression (76, 106). Some differences in strain response to SIF have been also described (25). Thus, affective aggression appears to be modulated by genetic factors.

Lesion and stimulation studies have provided evidence that certain brain areas are responsible for eliciting or inhibiting affective aggression (3, 33, 35, 139, 140). The amygdalar complex (AMY) and the nucleus accumbens septi (NAS) are the brain structures of essential importance for the control of affective behavior. The latter structure is supposed to act as an interface between the limbic emotion-controlling centers and the motor system (79, 120). Both structures are innervated by monoaminergic neurons originating in the mesencephalon, which contain DA, NE and 5-HT (7, 81, 82). Much research has been directed towards determining the role played by each monoamine in affective aggression. Pharmacological studies using systemic drug administration or toxin injections provided evidence of 5-HT-mediated suppression of the behavior (31, 49, 100, 130). DA, on the contrary, appears to enhance affective aggression (7, 15, 36, 46), while the data on NE involvement are somewhat conflicting. Many studies suggest an inhibitory role for the amine (28, 32, 36, 46, 57, 122), but contrary and totally negative findings have been also reported (20, 29, 59, 109). Generally, almost all experimental models of affective aggression seem to involve DA neuron activation (see 87). It can be thus inferred that DA is the important transmitter for the expression of the behavior while the remaining amines play a modulatory role.

CENTRAL DOPAMINERGIC SYSTEMS

Observations presented below support the vital role played by DA in affective aggression. Spontaneously aggressive rats are characterized by elevated hypothalamic DA content as compared to nonaggressive animals (10). Pharmacological stimulation of dopaminergic receptors produces affective aggression (7, 40, 63, 76, 106) or facilitates its elicitation in different ways (5, 7). Intracerebroventricular DA enhances SIF (36). On the other hand blockade of dopaminergic receptors achieved with neuroleptics inhibits affective fighting in various models (28, 40, 56,
106). Long-term neuroleptic treatment is known to cause sensitization of postsynaptic dopaminergic receptors (98). If such chronic treatment is discontinued transmission in dopaminergic synapses is facilitated; hence augmented affective aggression can be observed both in experimental animals (37) and human subjects (113).

Ascending dopaminergic neurons form three main pathways innervating different forebrain structures. Cell bodies of the neurons within the ventral midbrain tegmentum form two groups with no evident partition between them, the laterally situated A9 group and the centrally located A10 (21). The nigrostriatal pathway arises from the A9 nuclei or substantia nigra. Efferents from the A10 nuclei constitute the mesocorticolimbic system innervating limbic structures such as NAS and AMY (mesolimbic part) and cortical areas (mesocortical part). The third dopaminergic system, tuberoinfundibular pathway arising from the A12 nuclei, consists of short neurons reaching the pituitary stalk and involved in the control of hormone secretion (82).

The nigrostriatal neurons modulate the locomotor activity and their function in the pathomechanism of extrapyramidal disorders is probably the best explored area in the research into the CNS. Several adverse symptoms of neuroleptic treatment (parkinsonism, late dyskinesia) are associated with the blockade of postsynaptic receptors in the striatum (121, 124). However, the antipsychotic activity of these drugs has been ascribed to the inhibition of transmission in the mesolimbic system (48, 114, 123). Some evidence points to this system as an important neural substrate of affective aggression. Electrical stimulation of the A10 region or NAS modulates aggressive reactions in cats (8, 42). Non-specific ablations of the NAS were shown to induce affective behavior in rats and enhance SIF (3). Dopaminergic mesolimbic system has numerous neural connections with other transmitter systems, mainly with the noradrenergic dorsal bundle originating in the nuclei loci coerulei (LC) and with serotonergic neurons ascending from the raphe nuclei (6, 81, 82). However, so far no systematic research has been conducted into the role of the mesolimbic dopaminergic neurons and their interactions in affective aggression. Therefore a series of experiments was carried out by the present author and co-workers in which affective aggression was studied in male Wistar rats after systemic or intra-structural injections of drugs or with particular monoaminergic neurons destroyed with specific neurotoxins administered into the selected brain nuclei. Neurochemical effect of the toxin injections was verified by HPLC-EC or spectrofluorimetrically and affective behavior was studied in the AIF or SIF paradigms.
EFFECTS OF SUPPRESSION OF CATECHOLAMINERGIC TRANSMISSION

Systemic drug administration

Pharmacological evidence in support of NE role in affective aggression has been controversial. Depletion of the amine in the CNS after 6-OHDA was found either to enhance SIF (28, 122) or have no effect in the test (20, 29). Suppression of noradrenergic transmission with clonidine (CLO), an agonist of adrenergic $\alpha_2$ receptors, known to inhibit NE release and NE neuron activity (2, 17), was shown to alleviate SIF (109). However, aggression in the SIF model was markedly enhanced after piperoxan, another drug blocking noradrenergic transmission due to the antagonistic action at the postsynaptic $\alpha$ receptors (109). Contradictory results were achieved with CLO in the AIF model — the drug reportedly enhanced aggression after acute administration whereas injection of the preferential $\alpha_1$ receptor antagonist fenoxymezamine inhibited fighting in the model (18, 38, 106). Prolonged administration of CLO in drinking water also potentiated AIF (46). It is also worth mentioning here that in a double blind clinical trial CLO was found to exaggerate aggressive reaction in schizophrenic patients (50).

Direct administration of NE into the brain ventricles suppressed SIF, contrary to the effect of DA (36). Therefore some data point to the inhibitory role of NE, while other evidence suggests a facilitatory role of the amine in affective fighting. The picture is further complicated by the fact that CLO given in high, nearly toxic doses can induce aggression (74, 84). The effect is attributed to the stimulation of postsynaptic $\alpha_1$ adrenoceptors (40). However, the behavior resembles the pathological aggressiveness of the offensive type which is accompanied by marked hyperreactivity rather than a typical defensive reaction.

In our experiment the effect of acute and prolonged 7-day treatment with CLO or another $\alpha_2$ agonist S-3341 on affective aggression in the AIF test was verified (90). Both drugs given acutely did not change aggressive score, though rats treated with CLO revealed some tendency to react with enhanced aggression to APO. Prolonged administration of each drug significantly augmented aggression, the effect being in line with the study by Hahn et al. (46).

In another study (Pucilowski and Kostowski, to be published) rats were administered either CLO or prazosin, an $\alpha_1$ adrenoceptor antagonist more specific than phenoxybenzamine, for 14 days. The drugs were given to rats selected as non-aggressive according to their response to APO in a pre-test. When APO was injected to the animals 2 h after the drug treatment had been discontinued marked potentiation of AIF was observed in both drug groups as compared to saline-treated controls.
In one group APO was injected 48 h after termination of CLO treatment, and no signs of aggression were noted similarly to all control groups. Therefore, inhibition of noradrenergic transmission, both presynaptically (CLO) and postsynaptically (prazosin) mediated, seems to augment affective aggression. Lack of the effect 48 h after CLO treatment withdrawal is an evidence against the possible interpretation of the CLO effect as a consequence of development of postsynaptic adrenoceptor supersensitivity.

NE is an important transmitter modulating the activity of other monoaminergic systems (2). The noradrenergic ascending projection forms two pathways, the dorsal and the ventral bundle, differentially affecting various neurochemical and behavioral processes (56). This may explain the discrepancies in the evidence for NE role in affective aggression. The present results suggest that the central noradrenergic neurons suppress affective DA-related aggression through stimulation of the α₁ adrenoceptors. Further evidence in support of this notion is supplied by other experiments.

Isolation and prolonged ethanol administration

Chronic isolation of 4-6 week duration is a well known method of facilitating aggression (129, 132). Enhanced aggressiveness is interpreted as a result of the diminished inhibitory serotonergic and noradrenergic control (128, 130). Additionally, some evidence has been published demonstrating that isolated rats reveal an increased number of postsynaptic dopaminergic receptors (44). Therefore enhanced aggression might be ascribed to the diminished 5-HT- and NE-mediated negative control on one hand, and the facilitated dopaminergic transmission on the other.

Aggressive reactions are observed also during acute ethanol (Et-OH) administration (18, 61, 77, 78). Chronic Et-OH intoxication induces changes in dopaminergic receptor sensitivity and 5-HT neuron activity similar to those observed in isolated animals (61, 67, 68, 128).

We checked the intensity of aggression after APO in pairs of rats either isolated for 6 weeks or treated with Et-OH (5 g/kg daily in two doses as 20% solution v/v) orally for 21 days. The animals used in these experiments were classified as low-aggressive. It was found that in these rats following isolation, APO administration, dose-dependently induced aggression (Fig. 1). Also Et-OH-treated animals, tested 12-14 h after the treatment had been discontinued, revealed marked aggression following APO injection, in contrast to control water-treated group (94). The results confirm suggestions that sensitization of dopaminergic postsynaptic receptors and a decrease in serotonergic transmission play a permissive role in the affective aggression induction even in a subpopulation of non-aggressive animals.
Chemical lesions

In another study we investigated the effect of chemical, 6-OHDA-induced, ablation of A10 nuclei on SIF (89). A direct injection of the toxin into the A10 region was found to induce a specific DA depletion in the forebrain accompanied by a marked decrease in the aggression score. Thus it confirmed the suggestions that integrity of the mesolimbic system was essential for the full expression of affective fighting.

As already stated NE influence on affective aggression appears to be of inhibitory nature. The effect has been attributed to the neurons of the LC origin (32, 57), while the other ascending pathway, the ventral bundle, reportedly has more of a facilitatory role (59). Not long ago the peripherally administered noradrenergic toxin DSP-4 was demonstrated to augment SIF (80), and the toxin is known to affect primarily the LC
projection after systemic injection (51). In order to obtain more direct evidence in support of NE LC-mediated inhibitory influence on affective aggression we investigated AIF in rats after direct injections of 6-OHDA into the LC (91). The toxin caused selective NE depletion in the injection site and in the forebrain. APO given in a subthreshold dose to induce fighting in control, sham-operated animals elicited marked aggression in 6-OHDA-treated rats. The results confirmed the earlier suggestions that the noradrenergic neurons of the LC played an inhibitory role in affective aggression (32, 57). Furthermore we demonstrated that chemical destruction of noradrenergic LC neurons prevented the elevation of 5-HT (and 5-HIAA) concentration in response to APO. The observation supports the notion that serotonergic neurons may function as a link between noradrenergic influences on DA-related aggression (46).

EFFECT OF CHEMICAL LESION OF THE SEROTONERGIC RAPHE NUCLEI

The following experiments were aimed at elucidating which of the two main ascending serotonergic pathways, the mesostriatal system of the dorsal raphe nucleus (DR) and the mesolimbic system of the median raphe (MR), were responsible for 5-HT-mediated suppression of affective aggression. Ample evidence supports the hypothesis that the brain 5-HT function is to suppress various behavioral responses, aggression included (88, 116, 130). Drugs that stimulate serotonergic receptors or enhance amine synthesis are known to alleviate affective aggression in different models (15, 30, 102, 103, 107, 109). If serotonergic transmission is suppressed, this results in augmented affective fighting (29, 49, 102, 109, 110). It has been found that in muricidal aggression an inhibitory effect is exerted only by the DR neurons (see 88). This reaction, rat killing a mouse, has been widely used as a model of predatory behavior, a distinct category of aggression by both behavioral and neurophysiological criteria (52, 99). Also electrolytic lesion of this nucleus, but not the MR, has been shown to augment SIF (49).

In our experiments each of the two raphe nuclei was destroyed by injecting the serotonergic toxin 5,7-dihydroxytryptamine (5,7-DHT) into the structure. The effect of such treatment on AIF is shown in Fig. 2. Only DR-operated rats were reacting with marked aggression to a low dose of APO. In the second experiment we examined the effect of such lesions on AIF in rats treated with CLO for 7 days. Concomitant CLO treatment and DR ablation were found to be capable of inducing some aggressiveness also in the absence of APO injection. Additional administration of 2.5 mg/kg of APO elicited aggression in all groups, i.e. DR, MR and sham-operated. However, in the DR-destroyed rats the aggres-
Fig. 2. The effect of 5,7-dihydroxytryptamine-induced lesion of the raphe nuclei on AIF. Mean ± SEM from 5 pairs per group. APO was given in a subthreshold dose (2.5 mg/kg i.p.) to induce fighting in sham-operated rats (SH). Other details see Fig. 1.

The role of NAS

Further experiments were carried out in order to provide data on the role of monoaminergic innervation of the NAS. Being the terminal area of the dopaminergic mesolimbic system and a structure of considerable importance for aggressive display according to nonspecific lesion and stimulation studies, the NAS receives also serotonergic and noradrenergic innervation. Thus it could serve as the site of interactions between these neurotransmitters in their effect on affective aggression. In order to investigate the effect on the AIF of the destruction of particular aminergic neurons we microinjected the following toxins into the structure: 6-OHDA with desipramine pretreatment to destroy DA terminals, 5,7-DHT (plus desipramine) to make 5-HT and DSP-4 to induce NE ablation. Each toxin produced a depletion of a relevant amine/metabolite in the injection area, though DSP-4 additionally decreased 5-HT content. Both 6-OHDA and DSP-4 injected animals revealed augmented response in the AIF, whereas 5,7-DHT had no effect on aggression in the high-aggressive animals. The low-aggressive rats did not show aggression after either treatment (96).
Thus destruction of dopaminergic terminals in the NAS augmented affective aggression. Such denervation produced an increase in responsiveness of animals to dopaminergic agonists, an effect attributed to sensitization of postsynaptic receptors (53, 120, 137). Destruction of serotonergic neurons in the structure had no effect on the AIF. Therefore it may be concluded that inhibitory serotonergic control is mediated via some other forebrain structure and not the NAS. Noradrenergic modulation of aggression by the latter is very likely. Further evidence in support of the notion was supplied by another study.

Experiments with systemically administered drugs, although closer resembling the clinical situation, do not provide information on the site of action of the compounds. It was mentioned before that neuroleptics block aggressive reactions in animal experiments (22, 25) and in the clinic (41, 47), and that their psychotropic action is attributed to the effect on dopaminergic transmission in the mesolimbic system (48, 114, 123). We wanted to investigate if their anti-aggressive activity is similarly mediated at the mesolimbic system terminals. Two neuroleptic drugs, sulpiride (SUL), a specific D₂ receptor antagonist and cis(Z)-flupentixol (FLU), preferentially blocking D₁ receptors (117), were micro-injected into the NAS 5 min before APO. Both drugs suppressed the AIF after peripheral administration, but only SUL exerted the effect in doses not affecting general activity (Fig. 3). Its anti-aggressive action

![Graph showing the effect of acute i.p. injection of neuroleptics on AIF.](image)

Fig. 3. The effect of acute i.p. injection of neuroleptics on AIF. Pairs of rats were injected with saline (C), (±)sulpiride, SUL (Dolorglet, Bonn) or cis(Z)-flupentiksol, FLU (Lundbeck, Copenhagen), 30 min before 10 mg/kg of APO. Mean ± SEM from 6 pairs per group. * = P < 0.05, .. = P < 0.02 vs. C (Mann-Whitney test).
therefore, appears to be more specific than that of FLU (22). Direct intraaccumbens injection of SUL potently inhibited all aggressive behavior parameters. FLU decreased the number of attacks but did not significantly affect vocalization or the total posturing time after APO. The findings suggest that aggressive behavior after DA postsynaptic receptor stimulation is mediated mainly through D₂ receptors, at least in the NAS (Pucilowski and Kostowski, to be published).

Apart from dopaminergic innervation also noradrenergic supply of the NAS is involved in the affective aggression control. In previous experiments DSP-4-induced NE depletion enhanced AIF, but selectivity of such treatment was not sufficient to prove the NE-mediated inhibitory effect on aggression in the NAS. Therefore we decided to inject NE and another α₁ adrenoceptor agonist 1-phenylephrine into the structure and check their action on the AIF. Each of them was found to potently suppress AIF (Fig. 4), thus confirming NE and α₁ postsynaptic receptors involvement in the inhibitory control of affective DA-mediated aggression at the NAS level. Noradrenergic innervation of the structure is of the LC origin (82); thus the dorsal bundle neurons appear to modulate affective aggression directly at this forebrain site. An alternative hypothesis might explain the pro-aggressive effect after chemical NE neuron ablation or prolonged CLO treatment in terms of the development of postsynaptic adrenoceptor supersensitivity. Inhibition of aggression after microinjections of α₁ adrenoceptor agonists is an argument against this
explanation. It might be concluded that disturbed noradrenergic transmission releases the inhibitory control over the dopaminergic neurons and that event is not compensated by the increased postsynaptic adrenergic receptor sensitivity. Neurophysiological evidence suggests that some tonic activity of LC neurons is necessary for the normal function of serotonergic DR neurons (9, 119). It is therefore possible that a decrease in LC noradrenergic neurons activity, induced by CLO or LC stereotaxic lesion, results also in suppression of 5-HT-mediated inhibitory control over affective aggression. This controlling function of DR projection must be accomplished at some other than the NAS forebrain structure. Some data suggest that the AMY may be a likely localization of such 5-HT influence on aggression.

THE ROLE OF AMYGDALA

**Serotonergic neurons**

The AMY, mainly its cortico-medial portion, receives dense serotonergic innervation from the DR (6). Electrical stimulation of the DR was shown to inhibit bioelectrical activity of amygdalar neurons (134), a similar effect was observed following 5-HT iontophoretic application to the AMY (118, 134). AMY is believed to be a brain structure vitally important for initiating aggressive reactions, both of affective and predatory nature (34, 52, 112, 125, 139, 140). One of the hypotheses claims that the structure functions as a center changing visual stimuli into impulses leading to the induction of emotional responses (69). Whether, in particular circumstances, aggression would be manifested depends on the inhibitory neuron function exerted by various parts of the AMY, as well as by other limbic structures controlling aggressive responses e.g. the NAS. Affective behavior reportedly is suppressed by 5-HT input to the AMY as 5,7-DHT-induced destruction of the amine-containing neurons within the structure can augment this type of aggression (31). In the study by Rodgers direct injection of the amine into the cortico-medial, but not baso-lateral, AMY was shown to inhibit the SIF (100). The effect, however, was accompanied by a marked decrease in pain perception that obviously influenced responsiveness in electric shock-elicited behavior.

Our own study was meant to repeat the experimental design of Rodgers, the difference being that in addition to 5-HT we used another 5-HT receptor agonist quipazine and the doses of the drugs were selected so as not to influence pain sensitivity (92). Both compounds significantly decreased the number of aggressive postures/attacks in the
SIF test. They also potently blocked muricidal aggression upon intra-amygdalar administration. It means that serotonergic innervation of the AMY plays an inhibitory role in both distinct categories of aggressive behavior.

**Noradrenergic neurons**

Some evidence supports amygdalar NE involvement in aggressive behavior modulation. Most data, provided by microinjection studies, suggest the inhibitory role of the amine in predatory aggression (111, 135). Affective behavior (SIF) reportedly was not influenced by direct intraamygdalar application of the α (phenotolamine) or β (sotalol) adrenoceptor antagonists (101). In our experiment DSP-4 was used to destroy noradrenergic neurons terminating in the structure (95). Because NE, similarly to 5-HT, may decrease pain sensitivity after intraamygdalar administration (85), we employed the AIF model. DSP-4 induced specific NE depletion in the AMY since a pretreatment with 5-HT uptake inhibitor citalopram had been employed. The NE decrease was accompanied by a significant increase in aggressive behavior parameters. Microinjection of NE and phenylephrine into the central AMY on the contrary, markedly suppressed AIF (95). In conclusion it might be said that noradrenergic terminals in the AMY inhibit affective aggression and the effect is mediated via α₁ adrenoceptors.

**DISCUSSION**

Experiments described in the present review were aimed at explaining whether, and to what extent, the central dopaminergic neurons of the mesolimbic system are involved in affective aggression. It has been demonstrated that the system constitutes an important part of the neural network activated during aggressive reaction. Affective fighting apparently can be fully manifested providing transmission in the system is undisturbed. Affective aggression is also influenced by the functional state of other regulatory pathways. Neurons directly related to the expression of affective reaction, e.g. mesolimbic dopaminergic neurons, are under negative control mediated by other systems, two of which have been described in this study. One is the serotonergic DR pathway executing its control function at the AMY level. An increase in the dopaminergic tonus, for instance associated with aggressive reaction, activates negative serotonergic feedback mechanisms. This notion is supported by ample biochemical and behavioral evidence (23, 24, 43, 54, 64, 70). When this serotonergic control is suppressed as e.g. during isolation, low tryptophan diet or due to pharmacological treatment (126,
dopaminergic neurons are disinhibited and affective aggression can be readily induced. The other inhibitory pathway is the noradrenergic dorsal bundle arising from the LC. Since it innervates various limbic structures, cortical areas and monoaminergic mesencephalic nuclei, it can exert its modulatory activity at different brain sites and over a wide variety of behavioral reactions (54, 56, 86). Activation of postsynaptic \( \alpha_1 \) adrenoceptors in the system leads to a suppression of aggressiveness at both NAS and AMY level. It is likely that noradrenergic LC neurons are functionally linked with the mesostriatal DR system facilitating its inhibitory control over the forebrain centers, e.g. AMY. This notion is supported by electrophysiological evidence of tonic noradrenergic stimulation of DR neurons activity (see 2). If this NE modulatory action is suppressed by CLO (9, 119), the 5-HT influence on behavior should decrease. Biochemically, APO-induced increase in 5-HT activity can be suppressed by CLO or chemical LC lesion (46, 91), further substantiating the interaction of three monoamine systems in regulating animal behavior.

The presented results and the hypothesis of significance of aminergic interactions for affective aggression control based on these data might prove to be directly linked to the clinical practice. The concept may help to understand the biological reasons for at least a group of instances of pathological aggression cases observed in the clinic. Secondly, it provides suggestions as to the methods of treatment of aggressive individuals and points to the possibility of occurrence of aggression as an adverse effect of pharmacotherapy, which, however, can be in most cases predicted. Aggression is one of the symptoms accompanying schizophrenia, affective disorders, epilepsy, personality disorders or neuroses. Also drug and alcohol abuse are frequently associated with pathological aggressiveness. Generally, morbid aggression is an outcome of disturbed function of the central inhibitory systems. The opposite situation, i.e. enhanced activity of certain aggression facilitating neural systems, is quite rare (128, 129, 131). However, it can occur in the case of opiate or Et-OH dependence. Both, if administered chronically cause the suppression of dopaminergic neuron function, which in turn results in the development of adaptive supersensitivity of postsynaptic receptors in these systems (39, 67, 68). Those mechanisms might be responsible for the symptoms of pathological aggression observed in persons dependent on Et-OH or opiates (18, 39, 66). Acute administration of morphine suppresses aggression while Et-OH augments it (19, 39, 77). The acute effect of small doses of Et-OH resembles that of anxiolytic drugs in aggression tests and is interpreted as a result of alleviation of inhibitory influences (e.g. 5-HT-mediated) on behavior (61, 77). In various clinical syndromes

129, 133),
malfuctioning serotonergic neural system has been described. The biological reasons are at times obvious e.g. lack of thiamine or tryptophan in the diet, although more often they remain unknown. However, in every case of the serotonergic system dysfunction violent aggression or autoaggression (suicidal attitude) is readily elicited (130, 131). In schizophrenia aggressive symptoms can be ascribed, similarly to many other manifestations, to the overactivity of mesolimbic dopaminergic transmission (114, 123). Whether this dysfunction is primary or secondary to some other processes remains a question open to research.

Still pathological symptoms, aggression included, are susceptible to neuroleptic treatment (16, 41, 47). These drugs are also the most potent remedies in violent behavior accompanying other diseases (41, 47, 75). Irrespective of the direct mechanism responsible for the appearance of aggression, neuroleptics provide an effective control of violent behavior by blocking the mesolimbic dopaminergic system function, one of the most important links in the neural network active during aggressive response. It remains disputable, whether the exact mechanism of their action involves motivational or rather effector motoric function. The latter possibility appears even more substantiated by available evidence, even if we accept the "switchboard" theory of the NAS (69, 79, 120). Motivational input from the higher limbic centers, the AMY and the hippocampus, is supposed according to this hypothesis, to be transformed in the NAS into impulses initiating appropriate movement action. These involve dopaminergic mechanisms in the NAS itself as well as in the neighbouring striatum. By blocking this effector dopaminergic link, neuroleptics may disable an individual to act out his aggressive attitude, while not changing the attitude itself. However, chronic neuroleptic treatment may lead to the opposite effect, i.e. facilitating or eliciting aggression in previously non-aggressive individuals (113). Experimental data point to the dopaminergic postsynaptic receptor supersensitivity development as the most likely reason for these abnormalities. Therefore pathological aggression would be a symptom of adaptive receptor alterations in the mesolimbic system, just as tardive dyskinesia is connected with adaptive receptor changes in the nigrostriatal system (121). It is of interest that concomitant lithium administration may prevent development of aggression during neuroleptic treatment (4). Lithium salts are, along with neuroleptics, widely used in the treatment of aggressive individuals (65, 109). Their effectiveness is explained by enhancement of tryptophan concentration in the CNS (12, 109) and by prevention of dopaminergic receptor supersensitivity development during prolonged neuroleptic treatment (4).
The fact that not only neuroleptics can enhance affective aggressiveness (upon withdrawal) can be observed following administration of various psychotropic drugs (27, 58, 60, 71, 127, 136). In the clinic aggressive reactions have been described after benzodiazepine anxiolytics or antidepressant drugs (45, 97). If the direct mechanism of benzodiazepine action is related to a different transmitter system than those described in the present study (GABAergic), aggression following antidepressants might be explained by current hypothesis. These drugs suppress affective aggression when given acutely (5, 22) and potentiate it with prolonged administration (27, 60, 71, 136). They also augment other behavioral responses commonly associated with the function of the dopaminergic mesolimbic system (e.g., 72, 115). It thus appears that one of the possible mechanisms of their action is facilitation of transmission in the mesolimbic dopaminergic synapses, which in turn makes aggressive behavior readily releasable.

Concluding, it may be claimed that every pharmacological manipulation which leads to a serious disruption of the functional balance between central monoaminergic systems is apt to influence emotional-aggressive behavior. We should realize that many non-psychotropic drugs may also affect central monoaminergic neuron function, e.g. caffeine and other xantines, digoxin and many hypotensive agents. Aggressive outbursts during their administration are fortunately infrequent (30, 50, 129), presumably owing to the multisystem negative control over aggression (5-HT, NE, GABA) (73, 131).

Experimental evidence convinces us that normally only a small percentage of population reacts with overt aggression to various, even strong, eliciting stimuli (25, 62, 73, 76, 105, 106, 129). Consequently, this behavior appears to be genetically determined. Affective aggression can be regarded as a natural behavioral response only under critical circumstances e.g. life threat. The individual reacting with aggression to every, even apparently neutral, stimulus is suspected of aberrant CNS function. The disorder most often involves the serotonergic transmission, while noradrenergic neurons innervating the limbic emotion-controlling structures might be also affected. That negative control is easily disturbed in a variety of pathological situations (128, 129, 131), this being a critical element which leads to the manifestation of pathological aggression. New methods of treatment should consider the possibility of "augmenting" the action of the inhibitory neurotransmitter systems. Agonists of serotonergic receptors, nowadays more readily available, are of interest in this respect. On the other hand one should act with great caution, when drugs potentially apt to release aggressiveness are to be prescribed for prolonged therapy, in outpatients in particular. For instance such
a high risk situation occurs when compounds suppressing serotonergic transmission are prescribed jointly with drugs known to interfere with noradrenergic transmission (e.g. CLO). Furthermore, adaptive receptor sensitivity changes should be taken into account when planning any long-term therapy with adreno- or dopaminolytic drugs.

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