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ROLE OF OPIOID RECEPTORS IN SELF-AGGRESSION IN RATS

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Abstract : Self-aggression is a behavioural disorder in which an individual damages its own body parts by intense biting or scratching. Self aggression has been reported in human patients in Lesch-Nyhan syndrome and in cases of schizophrenia, depression, and congenital analgesia. In human patients as well as in experimental animals some kind of dysesthesia of the part of the body that is mutilated has been suggested. This study was conducted to find out the underlying pain mechanisms in self-aggressive behaviour arising out of stereotypy.

The study was performed in 40 adult male rats. In all these animals, self-aggression was produced as part of amphetamine induced stereotyped behaviour. A predetermined scale was used for quantifying this behaviour. Reserpine and phenoxybenzamine pretreatment led to an increase in the incidence of self-aggression. Naloxone administration in reserpine pretreated animals led to a further significant increase in the incidence of self biting as compared to controls. From these studies it appears that self-aggressive behaviour may be associated with increased pain sensation.

Key words : self aggression stereotypy naloxone

INTRODUCTION

Self aggression, or the destruction of parts of one's own body, is an extremely bizarre phenomenon. It seems very unnatural that a person should damage or injure his own body, considering that the instinct of self preservation is very strong in both humans and animals. Many authors have attempted to make animal models to study this phenomenon of self aggression (4,7,8,10).

In these animal models self-aggression may manifest as self biting when the animal bites away the parts of its own body or the biting of the objects in the cage or cage bars may be so intense and continuous that the animal inflicts damage to its mouth and jaw which produce bleeding.

The kind of self aggression that we have studied seems to be related to the stereotyped behaviour induced by increase in dopaminergic activity (i.e. administration of catecholamine releasing agents, such as amphetamine). Initially stereotyped behaviour manifests itself as sniffing, which when the stereotypy is more intense, changes to licking or biting, which may progress to self biting.

It has been shown by several experiments that the transition from sniffing to licking or biting can be influenced by removal of non-dopaminergic, probably nor-adrenergic (NE) mechanisms. Several ways of prevention of nor-adrenergic mechanisms e.g. 6-OHDA induced destruction of NE neurons in brain and pharmacological agents such as reserpine, phenoxybenzamine, clonidine and diethyldithiocarbamate (DDC) have been employed to induce the self biting or self destructive behaviour as part of stereotyped behaviour (8). Self injurious behaviour has been seen in certain human conditions of hereditary sensory neuropathies. Animal models with loss of sensation from periphery either by dorsal root section (7) or by peripheral nerve section (4) have been created to study this phenomenon of self-aggression.

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METHODS

Adult male rats were chosen for the study. In each animal amphetamine was injected and the presence or absence of stereotyped behaviour was noted. Stereotyped behaviour was considered to be present if the score was 2 or above in the scoring system described by Creese and Iversen (3). The scoring system for biting behaviour was modified :0, no biting; 1, occasional biting: 2, frequent biting and keeping the forepaw in mouth for longer duration; 3, fast and forceful biting with bleeding from tissues; 4, in addition to 3 above one or more of the phalanx is removed.

In the second step norepinephrine action in the stereotyped behaviour was blocked by either depleting NE (by reserpine) or by blocking NE receptors (phenoxybenzamine) and the behaviour was noted. In the third step the action of endogenous opioids was blocked by giving naloxone before giving amphetamine (in animals in which NE action was already blocked) and the behaviour thus produced was scored.

The experiments were conducted in 40 adult male rats weighing between 150-250 gms. Groups of 3-4 rats were housed in one cage and were housed in the animal room of the Department of Physiology, All India Institute of Medical Sciences. Food and water were provided *ad libitum* except during experimentation. After reserpine treatment the animal was kept warm by placing heaters around and hypothermia was prevented.

Four sets of experiments were performed:

Groups I: Each rat was kept in a separate cage on the day of the experiment and was allowed to stay in that surroundings undisturbed for 3-4 hours. Amphetamine was injected in the dose of 5 mg/kg and the behaviour of the animal was scored after every ten minutes, the first reading was taken after 5 minutes of amphetamine injection.

One week after group I experiments either group II or group III experiments were performed alternately. Group II experiments were followed by group IV experiments after an intervals of one week.

Group II: The rats were pretreated with 7.5 mg/kg reserpine 24 hours before injection of amphetamine and the behaviour was scored.

Group III: The rats were pretreated with 5 mg/kg phenoxybenzamine one hour before injection of amphetamine and the behaviour was scored.

Group IV: In reserpinized rats (7.5 mg/kg reserpine), 5 mg/kg naloxone was given 20 minutes before injection of amphetamine and the behaviour of the animal was scored.

RESULTS

Stereotyped behaviour was induced in all the 40 rats and a large percentage of rats demonstrated self aggression. This behaviour was predominant in groups II, III and IV in which animals were preteated with different drugs before amphetamine administration (Fig. 1 and Table I).

It may be mentioned that mortality rate in rats due to self aggression was rather low and the animals usually recovered in 3 to 4 hours. Therefore, it has been possible to give different drug combinations in the same animal making comparison and analysis of behavioural response easy.

Group I

Amphetamine treated animals: Amphetamine was injected intraperitoneally in 40 rats, of which five rats developed self-aggression, manifested as self biting (Table I). These animals showed biting occasionally (score 1) which consisted of just keeping the forepaw in the mouth for a short duration. The other two rats showed frequent biting but no bleeding or tissue injury (score 2). After 3-4 hours all the rats were normal.

Group II

Reserpine treated animals : Reserpine was given in the same 40 rats, 24 hours prior to amphetamine injection, 7 days after group I experiments. All the rats showed sedation with reserpine. Five to 10 minutes after amphetamine injection the activity in rats was increased and stereotypy was induced in all the animals. Self aggression manifested as self biting was induced in 12 rats (30% of total) which is not significantly different, from group I animals as calculated by Chi-square test. The intensity of biting was varying in different animals (Table I). Occasional biting (score 1) was shown by 3 rats whereas continuous forceful biting (score 2) was shown by 2 rats without any bleeding or tissue damage. In 7 rats however, intense continuous biting of the forelimbs or hindlimbs (or both in some) was produced with blood oozing out from injured area (scroe 3). In one animal one phalanx was chewed away as the biting continued. The biting stopped at varying intervals in different animals ranging from one hour to four hours, after which all the animals were normal.

Group III

Phenoxybenzamine treated animals : Seven days were given for recovery after drug treatments in group II animals. Amphetamine treatment was preceeded by phenoxybenzamine treatment in the same 40 rats. Self biting of varying intensities was seen in 12 animals (30% of the total). Phenoxybenzamine treatment did not alter self-aggression produced as compared to only amphetamine treatment as calculated by Chi-square test. Occassional biting of the forelimbs was observed in four rats (score 1) and continuous forceful biting without any bleeding or tissue damage was observed in 7 rats (score 2), one

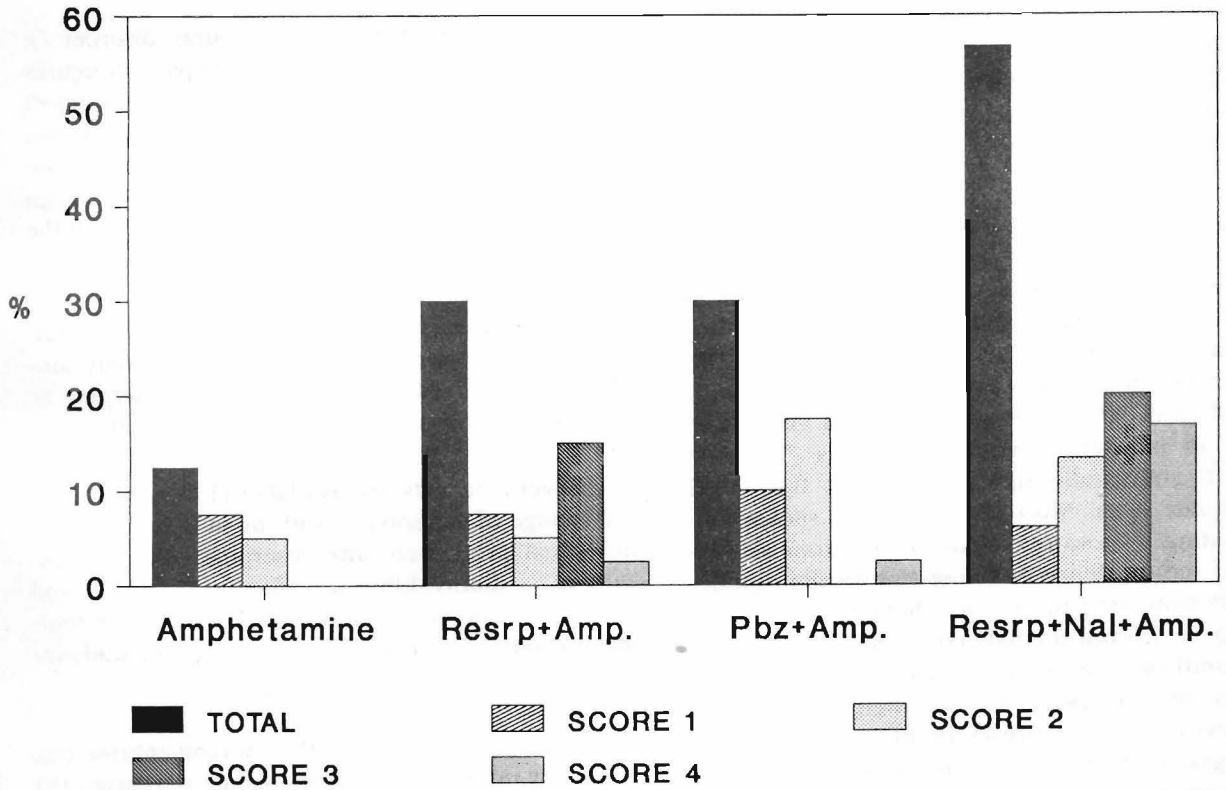

Fig. 1: Shows the percentage of rats showing various degrees of self-aggression with different drugs. Amp: amphetamine; Resrp: reserpine; Pbz: phenoxybenzamine; Nal: naloxone.

TABLE I : Effect of different drugs on self-aggression.

Group	*Treatment*	*Total No. of animals*	*No. of animal showing stereotypy*	*No. of animal showing self-aggression*	*No. of animals in biting score*			
					1	*2*	*3*	*4*
Gr I	Amphetamine	40	40	5 (12.5%)	3 (60%)	2 (40%)	0	0
Gr II	Reserpine + Amphetamine	40	40	12[a] (30%)	3 (25%)	2 (16.7%)	6 (50%)	1 (8.3%)
Gr III	PNZ + Amphetamine	40	40	12[b] (30%)	4 (33.3%)	7 (58.4%)	0	1 (8.3%)
Gr IV	Reserpine + PNZ Amphetamine	30	30	17[c] (56.7%)	2 (11.8%)	4 (23.6%)	6 (35.2%)	5 (29.4%)

a : Group I/II = 2.689; NS
b : Group I/III = 2.689; NS
C : Group I/IV = 13.535; S at P<0.05
Group II/IV = 3.984; S at P<0.05

rat continued biting for 3 hours and removed 2 phalanges in the process of biting itself (score 4).

Though the animals seemed to be recovering normally after the drug treatment, within a week a total of 10 animals were lost. The cause of death could not be determined.

Group IV

Reserpine and naloxone treated animals: In 30 reserpinized animals naloxone was given intraperitoneally before giving amphetamine. The number of animals showing self-aggression was increased from 30% in only reserpinized animals to 56.7% in naloxone pretreated animals (Table I) which is statistically significant at $P < 0.05$ level (Chi-square test). Most of the animals showed intense biting i.e. a score of 3 and 4. Naloxone also increased the incidence of biting statistically significantly as compared to only amphetamine treatment (Group I). Eleven animals continued biting vigorously unitl bleeding was produced (score 3) and 5 animals chewed away part of their forepaws or hindpaws (or both) (score 4). In three animals all the phalanges of the forepaw were chewed away. The biting continued for 4-5 hours in some animals. Two animals were found dead the next day.

DISCUSSION

Self-aggression is a behavioural disorder in which an animal attacks its own body parts or injures itself by some other means e.g. by biting an object such as cage bars so intensely that its oral apparatus is damaged. The reason why only self-biting was induced in our experiments could be that no foreign object was present in the plastic cages in which the animal was placed.

In our study there was an increase in the incidence of self-aggression from 12.5% in only amphetamine treated animals to 30% in reserpine as well as in phenoxybenzamine treated animals.

Several reports are available (1,8) which show the change of stereotyped sniffing in rats to self-biting when pretreated with reserpine, phenoxybenzamine, diethyldithiocarbamate (DDC) and 6-OHDA injection. Our results support these findings to some extent though these are statistically insignificant.

It has been suggested that norepinephrine has inhibitory influences on amphetamine stereotypy (6) which suggests that when NE action is prevented in stereotyped behaviour, release of inhibitor would

produce stronger stereotypy which as suggested by the authors is manifested as biting behaviour. Rodin and Kruger (11) report an increase in the average score of self-damage 90 days after 6-OHDA treatment is given neonatally.

From this study it is suggested that NE modulates self aggressive behaviour in rats.

When naloxone, an opioid receptor blocker, was given to 30 reserpinized rats the self-aggressive behaviour was produced in 56.7% animals. Intensity of self-aggression was also high in these rats. 64.6% animals showed intense biting with 29.4% animals manifesting tissue injuries along with bleeding.

Pert and Snyder (9) suggested that endogenous opioids are being released tonically. Injection of naloxone therefore, would reduce the effectiveness of the endogenous analgesic mechanisms and decrease the pain threshold. Hyperalgesia with naloxone, *per se* does not produce any change in the behaviour of the animal (5). The significant increase in the incidence of self-aggressive behaviour in the present study after naloxone treatment suggests that self-aggression is produced inspite of reduced pain threshold. On the contrary, reports are available (12) which suggest that analgesia of a region of the body stimulates self-biting as the animal perceives that part as a foreign object. Coderre et al (2) have reviewed various papers suggesting the self-mutilation of deafferented limbs as a response to chronic pain and dysesthesia. From the present study we conclude the association of increased pain sensation with self-mutilation phenomenon.

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