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EFFECT OF INTRACISTERNALLY ADMINISTERED ADENOSINE AND INOSINE ON APOMORPHINE-AND AMPHETAMINE-INDUCED STEREOTYPED BEHAVIOUR IN RATS

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Abstract : Apomorphine (2.5 mg/kg, ip)- and amphetamine 25 mg/kg, ip) - induced stereotyped behaviours were studied in rats pretreated with adenosine and inosine (12.5 nM/rat; volume, 10 µl, intracisternal injection).

Adenosine and inosine significantly antagonize the apomorphine - and amphetamine - induced stereotyped behaviour, presumably via modulation of nigrostriatal dopamine release.

Key words : adenosine inosine apomorphine amphetamine stereotypy

INTRODUCTION

It is now widely accepted that adenosine functions as an endogenous neuromodulator in both peripheral and central nervous system (CNS, 1). Adenosine is a normal constituent of the brain and is release from brain slices under certain conditions. A rapid rise of adenosine levels in the extracellular space following cerebral hypoxia (2), hypotension (3), seizures (4), and ischemia (5) have been demonstrated. Cerebral tissue stimulation results in the release of adenosine and smaller quantities of inosine hypoxanthine and other adenine nucleotides (6). Adenosine and adenine nucleotides inhibit spontaneous firing of neurons in virtually all brain regions (7). Adenosine has been shown to reduce amplitude of excitatory post synaptic potential (EPSP) in various parts of brain by an unknown mechanism (8) and inhibits the release of nearly all neurotransmitters, whether inhibitory or excitatory (9) Adenosine agonists have been shown to have sedative and hypnotic effects (10) and inhibit epileptiform activity *in vitro* (11). However, the physiological role of adenosine and inosine in the CNS is still unclear (1) and very little is known concerning the behavioural effects of adenosine and other nucleosides. The present study investigates the role of adenosine and inosine in apomorphine - and amphetamine - induced stereotyped behaviours in rats.

METHODS

Animals: Albino rats of wistar strain (HAU, Hissar, 120 - 140g) with free access to standard diet (pellets, Hindustan Lever Limited, India) and tap water were used. They were kept in an animal room under constant temperature (27±0.5°C), humidity and normal (12hr) light-dark cycle. Experiments were conducted between 10 and 15hr.

Apomorphine - induced stereotypy: Animals were divided into 3 groups of 10 in each. Group I served as control (treated with 10 µl normal saline intracisternally, i. cis.). In groups II and III adenosine and inosine (12.5 nM/rat, i. cis.) respectively, were given in a volume of 10 µl. Apomorphine (2.5 mg/kg, ip) was administered to all groups immediately after i. cis. treatment. Animals were observed for a 30 sec periods, every 15 min for a total period 2 hr and stereotypy was scored (12). Stereotyped behaviour was graded as follows; 1 - asleep or inactive, 2 - mild intermittent sniffing and head movements, 3 - sniffing with limited movements, some sniffing at the top of the cage, 4 - severe fighting alternating with leaping and running fast around the cage and some vocalization, 5 - wild fighting, leaping, persistent vocalization and bleeding from face and paws needing isolation, 6 - very severe fight-

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ing, leaping, bouncing at the top of the cage persistent vocalization and bleeding from face and paws needing isolation.

Amphetamine induced stereotypy : Rats were divided into 3 groups of 10 in each. Groups I served as control (receiving 10 µl normal saline, i. cis) just before amphetamine (25 mg/Kg, ip). In groups II and III adenosine and inosine 12.5 nM/rat, respectively were given in a volume or 10 µl, just before amphetamine administration. Each animal was than scored (13) every 30 min for a period 2hr as follows. Grade 0 - No activity, Grade 1 - normal activity, Grade 2 - increased motor activity, Grade 3 - stereotyped head searching, Grade 4 - continuous licking, Grade 5 - Mock bitting and/or Grade 6 - continuous gnawing.

In both types of experiments the mean stereotypy scores (control vs drug - pretreated groups) were compared by Student's 't' test (unpaired).

RESULTS

Apomorphine induced stereotypy : Adenosine and inosine significantly decreased apomorphine induced stereotyped behaviour in rats. The peak effect of both adenosine and inosine was observed after 90 min of intracisternal administration, although the onset of their action was rapid (Table I).

Amphetamine induced stereotypy : Both adenosine and inosine significantly antagonized amphetamine induced stereotypy. Though the effect persists for a shorter duration as compared to apomorphine experiments (Table I).

DISCUSSION

The nigrostriatal dopaminergic system has been recognised as being mainly responsible for the induction of stereotypy (14, 15, 16) and dopaminergic action of drugs is a prerequiste for induction of stereotypy. Adenosine is reported to inhibit the release of almost all neurotransmitters whether they are inhibitory or excitatory (9) viz, Ach (17), norepinephrine (18) dopamine (19) 5-HT (20). Therefore reduced release of dopamine by adenosine and inosine in the nigrostriatal system would be consistent with the reduction of stereotypy behaviour induced by apomorphine and amphetamine. Moreover, Rebeiro (21) and Wu et al (22) have reported that adenosine ATP, and other adenosine agonists decrease Ca^{2+} uptake by rat brain synaptosomes during K^{+} depolarization and these workers suggested that adenosine, ATP and other adenosine agonists exert their inhibitory effect on neurotransmission by inhibition of Ca^{2+} flux occurs at presynatic sites, it may reduce the release of brain neurotransmitters. Therefore, strong antagonistic effect of adenosine and inosine in apomorphine and amph-etamine induced stereotypy may be explained on the basis of decreased dopamine release in the nigrostriatal system due to inhibiting of Ca^{2+} dependent transmitter release mechanism, though this work not elucidate the mechanism involved in regulation of Ca^{2+} by adenosine and inosine.

TABLE I : Effect of adenosine and inosine (12. 5nM/rat, i. cis on apomorphine (2.5 mg/kg, ip) and amphetamine (25 mg/kg, ip) induced stereotypy in rats. Data represents — mean stereotypy score ± SEM of 10 animals for each drug.

	Stereotypy score/grades							
Drugs	*After 15 min*	*After 30 min*	*After 45 min*	*After 60 min*	*After 75 min*	*After 90 min*	*After 105 min*	*After 120 min*
Apomor	2.6±0.06	4.8±1.33	4.8±1.33	4.6±0.16	3.8±1.24	2.6±0.16	2.0±0.00	1.2±1.33
Adeno + Apomor	1.8±1.33***	2.2±1.33*	1.6±0.16*	1.2±0.33*	1.0±0.00**	0.8±1.33***	—	—
Ino + Apomor	2.0±0.00***	2.3±1.51	2.0±0.00*	1.4±0.16*	1.0±0.00***	0.6±0.16***	—	—
Amphe	—	4.3±0.21	—	4.5±0.22	—	4.2±0.19	—	3.9±0.27
Adeno + Amphe	—	3.3±0.15*	—	4.0±0.20***	—	3.5±0.16***	—	3.6±0.16***
Ino + Amphe	—	3.9±0.23*	—	4.5±0.20***	—	4.1±0.17***	—	3.8±0.13***

* P < 0.01, ** P < 0.05, *** P > 0.05, when compared with controls (Apomorphine, Amphetamine 't' test, unpaired).
Apomor-Apomorphine; Amphe-Amphetamine, Adeno-Adenosine; Ino-Inosine.

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