SHORT COMMUNICATION

ANORECTIC EFFECT OF SK & F 38393, A NEW DOPAMINE AGONIST IN RATS

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Summary : Anorectics are clinically used in the management of obesity to accept dietary restriction through decreased desire of food intake. The present study, indicates that the drug SK & F 38393 a dopamine agonist given to albino rats at the doses of 1 *mg/kg* and 5 *mg/kg* caused decreased food intake. Central side effects observed with amphetamine and other related drugs were not observed with this drug. The drug thus may be used as an anorectic agent without central side effects.

Key words : body weight food intake spontaneous motor activity

INTRODUCTION

The role of central adrenergic and 5-hydroxytryptamine systems in the regulation of food intake is well documented (3, 10, 11, 13). The role of dopaminergic system in the regulation of food intake has been demonstrated in recent studies and some of the central effects of amphetamine are also ascribed to its dopaminergic activity (4). Amphetamine, like apomorphine, produces aggressive behaviour (8) and stereotype motor activity in rats (5, 6). Carruba *et al.* (5) have demonstrated a decrease in food intake in rats pretreated with apomorphine, mazindol, bromocriptine and piribedil; and the action has been shown to be antagonized by specific dopamine receptor blockers.

In the present study a new dopamine agonist SK & F 38393 (2, 3, 4, 5--tetrahydro-7, 8 dihydroxy-1 phenyl-1H-3 benzazepine), which has been shown by Pendleton *et al.* (9) to produce renal vasodilatation by selective dopamine receptor activation, has been studied. This compound has been reported to be free from certain central side effects observed with the well known dopaminergic agonists, viz., emesis, stereotype motor activity and inhibition of prolactin release (12). Hence its anorectic activity has been investigated in rats. Its possible dopaminergic activity was validated by the use of pimozide, a dopamine receptor blocking agent.

MATERIALS AND METHODS

Albino rats, weighing 100-250 g, placed each in a separate cage, were trained to take food for 4 hr a day (9 a.m. to 1 p.m.) for 7 days with free access to water. At the time of the experiment the animals were given weighed quantity of food (Bengal gram soaked overnight in water) 15 min after the intraperitoneal administration of the drug in test group and saline in control group of animals. The remnants of food were weighed to calculate the consumption.

SK & F 38393 was dissolved in sterile distilled water and administered at a dose of 1 *mg/kg* and 5 *mg/kg* for 7 days. Pimozide dissolved in weak tartaric acid was administered at a dose of 0.5 *mg/kg*, ip and its effect on food intake and body weight was observed for 7 days.

In a separate group of 5 rats, the effect of SK & F 38393 (5 *mg/kg*, ip) was studied one hr after administration of the above dose of pimozide on food consumption and body weight. Food consumption in rats was calculated as g/100 g of body weight of the animal.

Another group of rats weighing 100-250 g were allowed to take food and water *ad lib*. Body weights were recorded daily. Spontaneous motor activity (SMA) was recorded for 90 min daily for 10 days on a kymograph by placing the animal in a triple-beam balance and the pointer of the balance was adjusted to zero and connected to a sensitive Starling heart lever.

SK & F 38393 was administered at a dose of 5 *mg/kg* orally daily for 10 days and SMA and body weights were recorded daily, and for 10 days after withdrawal of the drug.

SMA was also recorded in one group of rats after the administration of SK & F 38393, 5 *mg/kg*, ip. The results were analysed statistically by applying Student's 't' test.

RESULTS AND DISCUSSION

SK & F 38393 (1 *mg/kg* and 5 *mg/kg*, ip) reduced the food intake significantly ($P<0.01$ and $P<0.001$ respectively) in rats in a dose-dependent manner (Table I).

Significant reductions in body weights were also observed. The mean increase in the body weights of 10.26±1.6 g in control animals after 7 days saline administration, fell down to 4.13±0.77 ($P<0.05$) after the administration of SK & F 38393, 1 *mg/kg*, ip daily for 7 days. At the dose of 5 *mg/kg*, ip for 7 days there was a decrease in body weight (5.35±0.64; $P<0.001$). In these doses the drug did not produce any apparent change in behaviour or motor activity, viz., stereotype behaviour. Pimozide (0.5 *mg/kg*, ip), a specific dopamine receptor blocking agent did not have any effect on the food consumption. This dose also did not produce any apparent neuropletic activity, viz., catalepsy or ptosis, but it completely abolished the reduction in food intake induced by SK & F 38393 (Table I).

TABLE I : Decreased food intake induced by SK & F 38393 in albino rats and its reversal by pimozide.

Treatment	*Dose mg/kg (ip)*	*No. of animals*	*Food consumption g/100 g of body weight±S.E.*	*% change and significance*
Saline	—	7	16.98±1.75	—
SK & F 38393	1.0	5	11.18±0.35	34.15 $P<0.01$
SK & F 38393	5.0	5	6.15±1.01	63.78 $P<0.001$
Pimozide	0.5	5	15.44±0.24	Not significant
Pimozide and SK & F 38393	0.5	5	15.63±2.40	Not significant

Oral administration of SK & F 38393 at the dose of 5 *mg/kg* daily for 10 days also produced significant decrease in the body weight when food and water were allowed *ad libitum*. The mean increase in body weight was 13.6±2.2 g after 10 days oral saline treatment. After SK & F 383935 *mg/kg* orally for 10 days, there was a mean decrease in body weight of 4.54±0.63 g ($P<0.001$). Ten days after the withdrawal of the drug an increase in the body weight was observed (mean 12.31±2.69 g ; $P<0.01$). No significant change in the SMA was observed. SMA was also not significantly affected after the administration of SK & F 38393, 5 *mg/kg*, ip.

SK & F 38393 is a new dopamine receptor agonist (7). which does not share some of the central actions of other dopamine agonists like apomorphine and amphetamine as it does not produce emesis, stereotype behaviour and decreased prolactin activity (12). The known anorexiant, amphetamine has been known to reduce the food intake in rats and this effect was shown to be antagonized by pimozide, a specific dopamine receptor blocking agent (2). Similar action of bromocriptine, piribedil, lisuride, apomorphine

and amphetamine on food intake in rats has been observed by Carruba *et al.* (5) who postulated that the effect is modulated through activation of dopamine receptor sites.

Our results with SK & F 38393 support the role of dopaminergic system in the regulation of food intake as pimozide in the dose used selectively blocks dopamine receptors (1, 7) and it also completely abolished the action of SK & F 38393 on food intake. Research in developing new anorectic drugs is directed to minimizing the central side effects while preserving the anorectic activity. SK & F 38393 does not seem to produce excitation, emesis, stereotype behaviour or decrease in prolactin activity (12), and SMA. The site of action, therefore, remains intriguing. It is, however, possible that the central effects of dopamine are not significantly excitatory.

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