SPECIES DIFFERENCES IN EFFECTS OF APOMORPHINE AS AN ADRENERGIC AGENT*

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Apomorphine which, according to Belen'kii (1964, 1966), inhibits catechol-o-methyltransferase in cats and produces manifestations of adrenergic excitation in cats and rabbits, produced motor excitation, aggressiveness, and hyperthermia in rabbits and to a lesser degree in rats, but had the opposite effect in mice. Hypothermia is observed in mice after administration of various doses of apomorphine intraperitoneally, subcutaneously, intravenously, and into the cerebral ventricles. In rabbits and rats the effects of apomorphine are similar to those of amphetamine, while in mice they are opposite in nature. It is postulated that in mice apomorphine produces accumulation mainly of adrenalin, but in rabbits and rats it produces accumulation mainly of noradrenalin.

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It has been suggested by M. L. Belen'kii [1, 2, 4] that apomorphine inhibits the enzyme catechol-o-methyltransferase (COMT), and that its effects are therefore adrenergic in nature. Subsequent experiments on cats [3] showed that apomorphine reduces the excretion of 3-methoxy-4-hydroxymandelic acid after adrenalin loading. Pharmacological evidence in favor of this hypothesis is the potentiation and prolongation of the effects of adrenalin and noradrenalin in cats and to effects in rabbits qualitatively similar to those of amphetamine: hyperthermia and motor excitation [2, 4]. The similarity between the effects of amphetamine, liberating noradrenalin in the tissues, and of apomorphine, inhibiting COMT has a common biochemical basis, namely as excess of free catecholamines.

Since the hyperthermic and stimulant effects of amphetamine have been studied mainly in mice and rats [6, 9], it was decided to continue to compare the effects of apomorphine and amphetamine on animals of those two species. Rabbits were used for comparison. One of the most characteristic effects of amphetamine on mice kept together is aggressiveness. For this reason, special attention was directed toward the possibility of onset of aggressiveness in all 3 species of animals under the influence of apomorphine. Besides apomorphine and amphetamine, pyrogallol was investigated as the most extensively studied COMT inhibitor.

EXPERIMENTAL METHOD

Experiments were carried out at two seasons of the year on 2000 noninbred mice of both sexes weighing 18-25 g, 104 male rats weighing 250-350 g (62 Wistar rats and 42 noninbred), and 21 chinchilla rabbits of both sexes weighing 2.5-3.1 kg.

The freshly prepared aqueous solutions of the drugs were injected intraperitoneally or subcutaneously.

The motor activity of the mice and rats was recorded quantitatively by means of an electronic integrator [5], and the activity of the rabbits was recorded visually. Mean readings of the integrator counter for the first 15 min of the animals' stay in the chamber were used for the calculation.

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TABLE 1. Behavioral Responses and Body Temperature of Animals of Different Species after Administration of Apomorphine, Amphetamine, and Pyrogallol

Effect	Animals	Apomorphine (5-10 mg/kg)	Amphetamine (5-10 mg/kg)	Pyrogallol (25-50 mg/kg)
Motor activity	Mice	Reduced	Increased	Reduced
	Rats	Unchanged or increased	"	Unchanged
	Rabbits	The same	"	"
Aggressiveness in the group	Mice	Absent	Intense	Absent
	Rats	Well marked	Absent	"
	Rabbits	Perceptible	Perceptible	"
Rectal temperature	Mice	Reduced	Increased	Reduced
	Rats	Unchanged or increased	"	Unchanged
	Rabbits	The same	"	Reduced

Aggressiveness in mice after administration of amphetamine took the form of the phenomenon of group toxicity: motor excitation, bursts of rage, fights, biting. To study aggressiveness, the male mice were placed in groups of 10 in boxes made of organic glass measuring 10 × 20 × 20 cm. The rats were placed in groups of 5 or 10 in plywood boxes measuring 58 × 58 × 20 cm. Aggressiveness in these animals after administration of apomorphine, just as in mice after injection of amphetamine, was expressed as frequent assumption of a fighting posture, bursts of rage, and biting.

Aggressiveness developed in the rabbits after injection of apomorphine in the form of "staying put" when two rabbits met each other on the floor of the room. Usually one of the rabbits would attack and the other show a defensive reaction, hiding in the corner or running away.

The body temperature was measured in the rectum by means of a TSM-2 electrothermometer. The mean temperature was calculated for a group of 7-10 mice, 5-10 rats, and 3-4 rabbits.

EXPERIMENTAL RESULTS

The results in Table 1 show that the effects of apomorphine and amphetamine which were studied were qualitatively similar only in the rabbit and, to a much lesser degree, in the rat. Aggressiveness was often (but not always) observed in the rats after administration of only the smaller of the tested doses of apomorphine (2.5 and 5 mg/kg) and it resembled the picture of "group toxicity" of amphetamine in mice. The reproducibility of the phenomenon was higher in Wistar rats than in noninbred rats. In both noninbred and Wistar rats, in contrast to mice, amphetamine did not cause aggressiveness despite the use of special measures increasing the excitability of the central nervous system [7].

The body temperature of the rats was unchanged after most of the doses of apomorphine used, but small doses (2.5 and 5 mg/kg) produced an increase in temperature of 1-1.5° compared with the control (distilled water).

As Table 1 shows, all three effects of apomorphine in mice were opposite to those of amphetamine, distinguishing the mice from the rats and, even more so, from the rabbits. The motor activity (locomotion) of the mice was reduced after administration of apomorphine in doses of between 1 and 100 mg/kg (LD_{50} by intraperitoneal injection 260 mg/kg). In some experiments 3-5 min after intraperitoneal injection of 50-100 mg/kg apomorphine into groups of mice a transient (lasting 5-10 min) motor excitation accompanied by squeaking developed. After intravenous injection of apomorphine no motor excitation was observed. It was probably connected with the action of apomorphine solutions on the peritoneal receptors.

If the motor activity is recorded under conditions allowing for an oscillatory movement of the object (chamber, platform, etc.) where the mice were kept, the higher readings of the counter when recording activity of mice receiving apomorphine compared with the controls can be explained not by excitation of locomotion, but by the powerful and constant stereotyped movements of the limbs (scratching, scraping) and head. This was the case also in our experiments. We noted that during the first minutes that the mice were

in the chamber, when locomotion was inhibited under the influence of apomorphine and no stereotypes had yet developed, the readings of the counter were lowered. When, however, stereotyped movements were added [the mice stood up on their hind legs, supporting themselves with their forelimbs against the walls of the chamber (container), often looking over them], the readings of the counter quickly increased. The counter readings were thus opposite in nature depending on whether motor activity was recorded only during the first few minutes or over a longer period, and with or without a container.

The only investigation in which an increase in motor activity of mice under the influence of apomorphine (1 mg/kg) was found was carried out by means of an oscillatory recording system such as in the present experiments. It can therefore be concluded that the author cited did not record an increase in locomotion, but a stereotype.

Hypothermia was the most stable and reproducible effect of apomorphine in mice. It was produced by doses exceeding 1 mg/kg, and was about equal in level (5-6°) when produced by doses ranging from 1 to 100 mg/kg. With an increase in dose, only the duration of the hypothermia increased. Doses of 5-20 mg/kg gave the maximal lowering of temperature after 30 min, and it was restored after 2-2.5 h. Hypothermia also developed after injection of apomorphine into the cerebral ventricles of a mouse.

The opposite nature of the effects of apomorphine and amphetamine in mice, and the difference in this respect between mice and rabbits and rats do not rule out the probability that the action of apomorphine in mice is adrenergic in nature, because other adrenergic agents (adrenalin, noradrenalin, and pyrogallol – a COMT inhibitor), when administered in the same way, produced effects in mice qualitatively similar to those of apomorphine. When injected intravenously into mice, apomorphine caused hypothermia while noradrenalin and pyrogallol caused hyperthermia or no change in body temperature, and adrenalin caused hypothermia (but in maximal doses a very slight increase in temperature). If, therefore, apomorphine produces accumulation of a catecholamine in the blood as the result of inhibition of COMT, it can only be adrenalin and not noradrenalin. It may be that the opposite nature of the effects of apomorphine in mice and rabbits (and rats) is due to the fact that in mice it is mainly adrenalin which accumulates, while in rabbits, rats and, perhaps, cats it is noradrenalin.

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