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Dose-dependent behavioural changes induced by apomorphine in selected members of a primate social colony

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The effect of six acute doses of the dopamine receptor agonist apomorphine on non-human primate social and individual behaviour was studied in a social colony of four adult Stumptail macaques. Apomorphine was administered intramuscularly to 2 monkeys/day in doses ranging from 0·05 to 3·00 mg kg^{-1} 15 min before a 1 h observation period. Apomorphine induced hyperactivity, hypervigilance, and stereotyped behaviour at doses of 0·50 mg kg^{-1} and greater in all 4 monkeys. In addition it also caused a dose-dependent disruption of normal behavioural patterns. Social grooming was eliminated while the submissive gestures were significantly increased. It also induced an increase in vocalizations and suppression of food forage behaviours. The results demonstrate the role of dopamine systems in the mediation of affiliative behaviour as well as motor behaviour in a primate species. Also, since similar behavioural changes are induced in this species during chronic (+)-amphetamine treatment, it is suggested that dopamine systems play a predominant role in amphetamine-induced behaviour in primates.

Chronic administration of (+)-amphetamine to volunteers results in a syndrome virtually indistinguishable from paranoid schizophrenia (Angrist & Gershon 1970; Griffith et al 1972; Bell 1973). With this in mind, investigators have used amphetamine to induce behavioural changes in numerous animal species in an attempt to create models of psychosis. One approach used considers the behavioural changes induced in selected adult members of non-human primate social colonies after administration of amphetamine (Machiyama et al 1970; Kjellberg & Randrup 1971; Crowley et al 1974; Garver et al 1975; Miller & Geiger 1976; Haber et al 1977; Schiorring 1977; Schlemmer 1977). Several of the amphetamine-induced behavioural changes in monkeys resemble human responses during amphetamine psychosis (Ellinwood 1971; Schlemmer et al 1978a).

These and other studies have implicated central dopamine systems in many of the bizarre behavioural changes induced by amphetamine. To better evaluate the role of dopamine systems in the mediation of primate behaviour, we have to examine behavioural changes induced in monkeys by the dopamine receptor agonist, apomorphine. Monkeys serve as a particularly good species for this study, not only because of their rich variety of social and individual behaviours, but also because they are insensitive to the emetic effect of apomorphine (Brizzie et al 1955; Peng & Wang 1962) which limits similar studies in man.

Of the reports on the effect of apomorphine on animal behaviour (Colpaert et al 1976) few have considered non-human primate behaviour. None have examined the effect of apomorphine on primate social behaviour. We have examined the behavioural changes induced in monkeys by six doses of apomorphine.

METHODS

Subjects. These were four adult Stumptail macaques (*Macaca arctoides*, also known as *M. speciosa*), one male and three females who had lived together in a social colony for more than six months. The colony was continuously housed as a group in a 1·5 × 2·5 × 3·5 m cage throughout. They received a generous supply of food (Purina Monkey Chow) early each morning and had free access to water.

Drug administration. During the experiment, each monkey in the colony received one i.m. injection of each of six doses of apomorphine HCl (Eli Lilly, Indianapolis, Indiana) 0·05, 0·10, 0·30, 0·50, 1·0, and 3·0 mg (salt) kg^{-1}, in ascending order at 9.45 am. Only two monkeys received apomorphine each day and at least 48 h separated each drug injection. At the same time, 0·9% NaCl (saline) was administered intramuscularly to those monkeys not receiving drug treatment. Saline was also adminis-

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tered to each member of the colony on four designated days during the experiment when baseline behaviours were established.

Behavioural observation. This began 15 min after drug and/or saline injection and lasted for 60 min. During that time, an experienced, 'blind' primate observer quantified and recorded the behaviour of each animal in the colony from a checklist of 48 social, solitary, and abnormal behaviours using the focal sampling technique in the following manner.

One monkey in the colony was observed for a 30 s interval. All behaviours displayed by the animal during that 30 s were recorded on the checklist during the following 30 s. Then, a second monkey from the colony was observed during the next 30 s and his/her behaviour similarly recorded. This process continued in rotation for a total of 12 30-s intervals. Each animal was observed once every 5 min for 1 h. Scores from the 12 30-s intervals were summed for each behaviour for the individuals and represented the daily score for each monkey. In addition, the total number of 'wet dog shakes', during the entire observation were recorded.

Statistical analysis. This was performed using a three-way partially crossed analysis of variance, and the least significant difference method for comparing means within the analysis. All data depicted are expressed as the mean score ± standard error of the mean for the four monkeys during each respective treatment period.

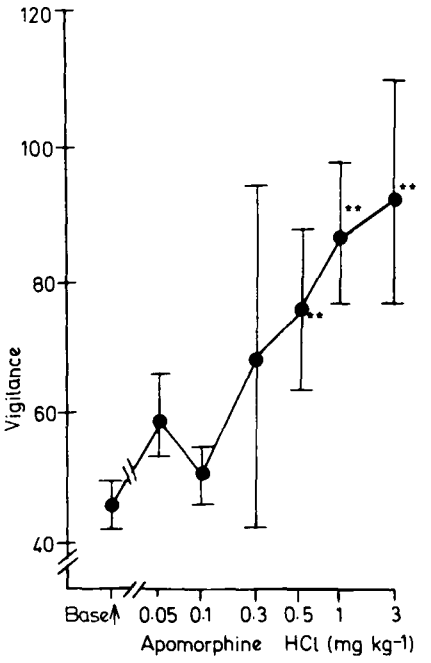

FIG. 1. The effect of six apomorphine doses on vigilance (checking) scores. Each point represents the mean vigilance score ± standard error of the mean (s.e.m.) for four monkeys during each respective treatment period. Statistical significance is denoted by: ** $P < 0.01$ when compared with the baseline (base) mean.

RESULTS

Baseline scores for each behaviour were within a normal range suggesting a stable social colony. In general, acute administration of apomorphine induced hyperactivity, particularly at higher doses. Both abnormal behaviours and alterations in normal behavioural patterns were induced by apomorphine.

Abnormal behaviour induced. As the apomorphine dose was increased, hypervigilance, or increased changes in visual field as determined by head and eye movement appeared first. Vigilance (checking) scores were significantly increased from baseline levels at doses of 0·50 mg kg^{-1} or greater (Fig. 1). Treated animals repeatedly looked around the cage in a random fashion, they did not appear to be 'tracking' imaginary objects as is occasionally seen after administration of some c.n.s. stimulants.

As expected, higher doses of apomorphine induced stereotyped behaviour (Fig. 2). The threshold dose was 0·50 mg kg^{-1}, while stereotypy became pronounced at 1·0 and 3·0 mg kg^{-1}. Several forms of stereotypy were noted including gnawing, licking, and self grooming. Tongue protrusion dyskinesias were seen in two monkeys at the two highest doses given.

Excessive scratching was seen in two monkeys following administration of 0·50 and 1·0 mg kg^{-1} of apomorphine, but was not noted at the 3·0 mg kg^{-1} dose.

Effect on normal behavioural patterns. Apomorphine also induced profound alterations in normal behavioural patterns. All doses eliminated social grooming (Fig. 3), a prominent affiliative behaviour in this species. One of the most dramatic effects was the significant increase in the number of submissive gestures (Fig. 4). At the two highest doses, some monkeys would lipsmack and retreat from almost any movement in the group cage. Both lipsmack and submissive present scores were elevated at these doses.

Apomorphine induced a significant increase in the number of vocalizations (Fig. 5). These were unusual in that they resembled a bark more than the typical higher-pitched sounds.

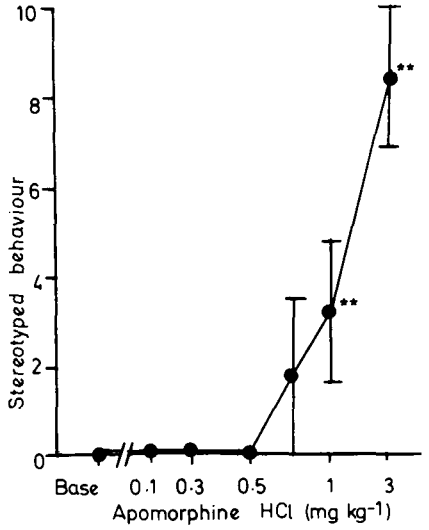

FIG. 2. The induction of stereotyped behaviour in monkeys by apomorphine. Each point represents the mean stereotyped behaviour score ± s.e.m. for four monkeys during each respective treatment period. Statistical significance is denoted by: ** $P < 0{\cdot}01$ when compared with the baseline (base) mean. Stereotyped behaviour was only seen after the three highest doses of apomorphine.

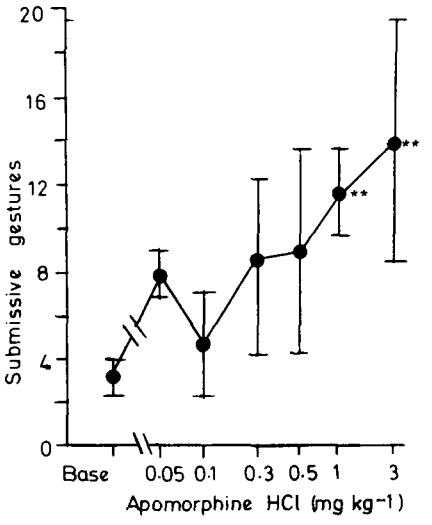

FIG. 4. The dose-dependent effect of apomorphine on submissive gestures given by treated monkeys. Each point represents the mean submissive gesture given score ± s.e.m. for four monkeys during each respective treatment period. Statistical significance is denoted by: ** $P < 0{\cdot}01$ when compared with the baseline (base) mean.

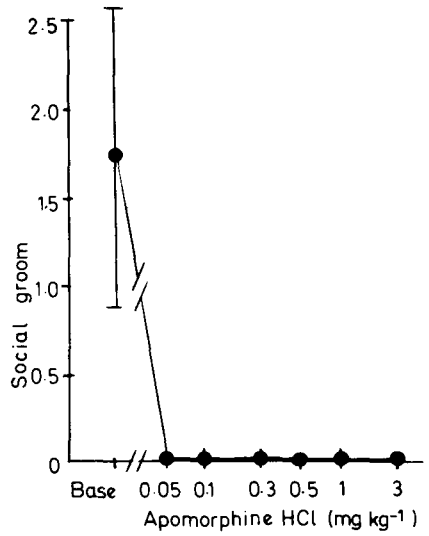

FIG. 3. The effect of apomorphine on initiated social grooming by monkeys. Each point represents the mean initiated social grooming score ± s.e.m. for four monkeys during each respective treatment period. Apomorphine eliminated social grooming at all six doses tested.

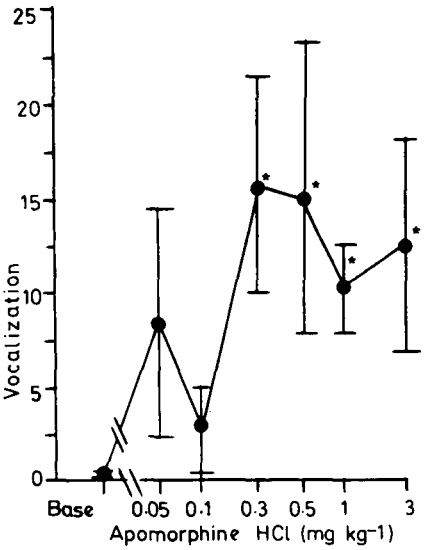

FIG. 5. The effect of six doses of apomorphine on vocalizations from monkeys. Each point represents the mean vocalization score ± s.e.m. for four monkeys during each respective treatment period. Statistical significance is denoted by: * $P < 0{\cdot}05$ when compared with the baseline (base) mean.

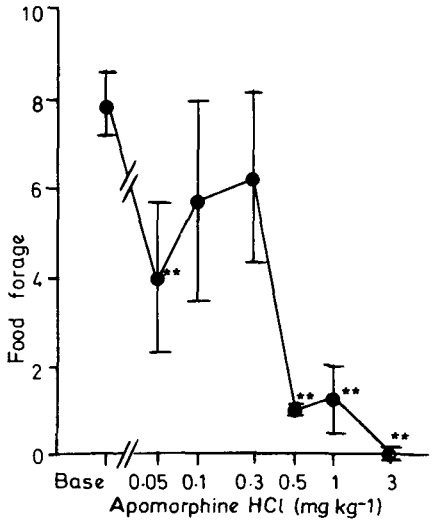

FIG. 6. The effect of six doses of apomorphine on food forage scores in monkeys. Each point represents the mean food forage score ± s.e.m. for four monkeys during each respective treatment period. Food forage scores include the sum score of three behaviours, handle food, chew food, and drink. All three behaviours showed a dose-dependent decrease with increasing doses of apomorphine. Statistical significance is denoted by; ** $P < 0.01$ when compared with the baseline (base) mean.

Apomorphine also induced a dose-dependent reduction in food forage behaviour (Fig. 6). Each of the three food forage categories, handle food, chew food, and drinking were decreased.

As important as the behaviours induced by apomorphine are those which were not seen following drug treatment. Emesis was absent, also, wet dog shakes or limb jerks, induced in this species by hallucinogens (Schlemmer et al 1977, 1978b; Tyler et al 1978), were not induced.

Several behavioural changes were induced in one monkey. These included increased distancing from and aggression towards other monkeys and increased locomotion. Apomorphine failed to significantly alter scores from baseline levels in any other behavioural category.

DISCUSSION

There is a large amount of evidence suggesting that apomorphine is a selective dopamine agonist (Colpaert et al 1976). Therefore, it is assumed that the behavioural changes seen in this study are mediated through dopamine systems. The results demonstrate the role of dopamine systems in the mediation of primate behaviour. Apomorphine not only induced abnormalities in motor behaviour (see Shintomi & Yamamura 1975), but also caused a major disruption of normal affiliative behaviour. Social grooming is a major component in the formation of social cohesiveness and its elimination constitutes one form of social withdrawal. It might be argued that social grooming was merely replaced by motor stereotypies induced by apomorphine. This appears unlikely for two reasons. First, social grooming was eliminated by doses of apomorphine (0·05–0·3 mg kg^{-1}) which are lower than those necessary to induce stereotypy. And secondly, from previous studies of chronic (+)-amphetamine administration to this species, we have noted that intense stereotyped behaviour is commonly manifested as grooming, particularly self grooming and occasionally social grooming. There was also a significant increase in the number of submissive gestures given by apomorphine-treated monkeys, who apparently perceived seemingly normal, non-threatening situations as threatening.

At first glance, these observations appear to be contradictory to the findings of Tamminga et al (1978) who found a transient, but significant improvement in the psychotic symptoms of chronic schizophrenic patients following apomorphine administration. However, the apomorphine dose given was approximately 0·05 mg kg^{-1}, a dose that failed to induce significant behavioural changes in monkeys with the exception of social grooming. Furthermore, these investigators postulated that the antipsychotic effect of apomorphine was probably due to presynaptic effects of the drug which inhibit dopamine release thereby causing a functional decrease in dopamine-mediated neural transmission (Tamminga et al 1978). On the other hand, the behavioural changes induced in monkeys by the higher apomorphine doses more than likely are due to an agonist effect on post-synaptic dopamine receptors. In support of this hypothesis is the appearance of stereotyped behaviour at doses of 0·50 mg kg^{-1} and greater. There is an abundance of animal data attributing the induction of stereotypy by apomorphine and a number of other c.n.s. stimulant drugs to the functional activation of central dopamine systems (Randrup & Munkvad 1970; Wallach 1974; Kelly 1977). Additional evidence was obtained in a pilot study where intramuscular injection of the relatively selective dopamine receptor blocking agent, haloperidol, 0·05 mg kg^{-1}, 2·25 h before apomorphine, 0·50 mg kg^{-1}, prevented the appearance of all apomorphine-induced abnormal behaviour in four adult stumptail macaques.

All of the major behavioural changes induced by apomorphine in this study constitute major behavioural changes in this species during chronic (+)-amphetamine treatment (Garver et al 1975; Miller & Geiger 1976; Schlemmer 1977; Schlemmer et al 1978a). Therefore, these findings provide additional support for the predominant role of dopamine systems in the mediation of many amphetamine-induced behavioural changes in primates.

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