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LETTER TO THE EDITOR

BIPHASIC EFFECT OF APOMORPHINE ON RODENT MOTILITY

Sir,

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The dopaminergic (DA) system has been implicated in a number of neurological and psychiatric disorders. In studying neurotransmitter systems such as the DA system in the laboratory animal, behavioural studies are commonly employed. Since behaviour is a sum total of a variety of internal and external excitations and inhibitions, in such studies it it necessary to use a chemical probe which specifically modulates one aspect of neurotransmission in order to understand the influence of that aspect of neurotransmission on behaviour. Apomorphine is one such probe, specific to the DA system.

Apomorphine is a direct DA receptor agonist (1,2) which in low doses inhibits and in high doses facilitates DA neurotransmission. It is suggested that the former effect is mediated by (presynaptic, inhibitory) DA autoreceptors and the latter by (facilitatory) DA post-synaptic receptors (3,4). In this report, this 'biphasic' (dose-related) effect of apomorphine on motility parameters in the rat is demonstrated.

Adult, male, Sprague-Dawley rats (200-250 g), housed two per cage with free access to tap water and standard laboratory diet, were brought into a temperature and humidity controlled, 12 hour light-dark cycle (lights on at 6 a.m.) sound-proof, insulated room one week prior to starting the study, and were maintained in this environment until the end of the experiment.

On a random basis, groups of rats (n=16 per group) received either low dose (100 μg/kg, ip) or high dose (2 mg/kg, ip) of freshly dissolved apomorphine (SIGMA chemicals), or vehicle alone (normal saline, 1 ml/kg, ip). The rats (one pair at a time) were then placed in separate Opto-Varimex (Columbus Instruments) monitoring chambers (42 cm×42 cm) which contain 15 infra-red emitters and sensors located on the x and on the y axes of the chambers. Interruptions of the infra-red beams are sampled at the rate of 4/sec and are analyzed in an interfaced Apple II plus computer using the Autotrack Programme. The data herein generated describe 8 motility parameters (see Table I).

TABLE I : Motility parameters in low and high dose apomorphinetreated rats, and in saline-treated controls.

Parameter	*100 μg/kg apomorphine (n=16)*	*2 mg/kg apomorphine (n=16)*	*Saline control (n=16)*
Distance travelled (in cms)	706.43 ±453.10(b)(1)	6022.68 ±3704.42(b)(1)	2327.25 ±1249.83
Time ambulant (in secs.)	63.0 ±42.9(b)(1)	561.31 ±318.14(b)(1)	186.56 ±92.4
Time spent resting (in secs.)	1494.43 ±167.06(b)(2)	479.31 ±311.69(b)(1)	1090.75 ±187.08
Time engaged in stereotypic behavious (in secs)	244.06 ±126.94(b)(2)	754.25 ±106.83(b)(2)	511.93 ±108.94
Number of bursts of stereotypies	398.37 ±204.8(b)(2)	1820.25 ±1419.01(a)(1)	817.93 ±213.93
Number of clockwise rotations	3.62 ±3.72(b)(1)	38.12 ±22.86(b)(1)	10.81 6.97
Number of anticlockwise rotations	4.18 ±3.12(b)(1)	36.43 ±24.29(b)(1)	13.37 7.11

(a) P<0.01 (in comparision with saline-treated controls)
(b) P<0.001 (,, ,, ,, ,, ,,)
(1) Fisher's exact probability (median) test
(2) Student's 't' test.

Motility was monitored in the 2 chambers simultaneously for a period of 21.25 min commencing 5 min after the injection. Monitoring was conducted during the mornings only (9 a.m. - 1 p.m.).

The results are presented in Table I. Apomorphine in low doses significantly depressed and in high doses significantly increased motility on all 8 parameters, as compared as compared with saline-treated controls.

This 'biphasic' effect of apomorphine on motility parameters in the rat has parallels in other animal substrates. For example, dose-related biphasic behavioural responses (ranging from activity to sedation) in the common marmoset have been reported (5), as also a variety of visually monitored dose-related biphasic behavioural effects (ranging from locomotion and exploratory activity to stereotypic behaviour) in rodents (6) Similarly, animal models of apomorphine-stimulated yawning have been characterized by a bell-shaped dose-response curve (7).

In 1974, Carlsson (2) proposed that in low doses DA agonists stimulate the (then hypothetical) presynaptic (inhibitory) DA autoreceptors while in high doses these drugs stimulate the (facilitatory) DA post-synaptic receptors. These suggestions are fully accepted today (3) irrespective of the receptor subtype (D_1 or D_2) or of the DA pathway (eg. mesolimbic or nigrostriatal).

These effects of apomorphine suggest that it would be a useful probe of DA autoreceptor and post-synaptic receptor function given the appropriate experimental modulation of the challenge dose.

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