J. Pharm. Pharmacol. 1980, 32: 571–576 Received April 29, 1980

On the ability of *N*-chloroethyl aporphine derivatives to cause irreversible inhibition of dopamine receptor mechanisms

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The potential dopamine inhibitory properties of (−)*N*-(2-chloroethyl)-norapomorphine [(−)NCA], (−)*N*-(hydroxyethyl)norapomorphine [(−)NHA], (−)*N*-(2-chloroethyl)-norapocodeine[(−)NCC] and 6-[2-bis-(2-chloroethyl)-amino]acetyl-11-acetoxy-2-hydroxy-10-methoxynoraporphine (**I**) were assessed in behavioural (ability to antagonize apomorphine climbing, stereotypy and circling after unilateral electrolesions of the striatum in the mouse, ability to initiate circling/asymmetry alone or after challenge with apomorphine when injected unilaterally into the striatum of rat) and biochemical (ability to inhibit the binding of [^{3}H] (−)*N*-n-propylnorapomorphine, ^{3}H-NPA, to rat striatal homogenates) tests. (−)NCA, 10–20 mg kg^{-1} s.c., antagonized apomorphine climbing for a period of 5 days, the response recovering to control values by the 7th day. 10 mg kg^{-1} s.c. (−)NHA, (−)NCC or **I** failed to modify apomorphine climbing. Similarly, 2–4 mg kg^{-1} s.c. (−)NCA caused a long-lasting inhibition of apomorphine circling in the mouse (up to 5 days) whilst (−)NHA, (−)NCC and **I** were inactive. (−)NCA (10–40 μg) (but not (−)NHA, (−)NCC or **I**) also caused ipsilateral circling/asymmetry when injected unilaterally into the striatum of rat: this effect was enhanced by apomorphine. However, all agents, including (−)NCA, failed to consistently modify apomorphine stereotypy in the mouse. Non-labelled (−)NPA, (−)NCA and (−)NHA were shown to inhibit the 'specific' binding of ^{3}H-NPA to rat striatal homogenates; (−)NCC and **I** were ineffective. A single washing removed the (−)NHA inhibition whilst repeated washing caused only a modest reversal of the inhibition afforded by (−)NCA. It is concluded that *N*-chloroethylation in the aporphine series can abolish dopamine agonist action and confer a long-lasting dopamine antagonist potential.

β-Haloalkylamine derivatives such as phenoxybenzamine which can inhibit noradrenergic transmission are considered to irreversibly bind to the noradrenaline receptor. This persistent receptor blockade has proved useful in functional analyses of noradrenaline agonist-antagonist action. The recent synthesis of a number of haloalkylamine derivatives in the aporphine series (Neumeyer et al 1980a,b), traditionally associated with dopamine receptor affinity (Kumar & Jain 1977), prompted an initial assessment of the ability of one compound, (−)*N*-(2-chloroethyl)-norapomorphine [(−)NCA], to inhibit dopamine function. These preliminary experiments have shown that (−)NCA can inhibit striatal dopamine function as indicated by behavioural (induction/antagonism of circling) and biochemical (inhibition of dopamine sensitive adenylate cyclase, inhibition of the binding of [^{3}H]-(*N*)-n-propylnorapomorphine, ^{3}H-NPA) studies (Costall et al 1980a; Neumeyer et al 1980b). These inhibitory effects are long-lasting, possibly irreversible, and may involve the formation of a reactive ethyleneimmonium cation which, when followed by ring scission, yields a reactive carbonium ion which can subsequently react with a nucleophilic centre located on the receptor. The present studies further assess the ability of (−)NCA to inhibit dopamine function in the rodent brain, and the importance of the *N*-chloroethyl substitution and the hydroxyl groups in the aporphine series for an effective interaction at the dopamine/neuroleptic receptor.

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MATERIALS AND METHODS

Behavioural assessments. The potential antagonist effects of *N*-chloroethyl and *N*-hydroxyethyl aporphine derivatives were assessed in three behavioural models using apomorphine in the mouse, climbing, stereotyped and circling behaviour. In each model the onset of the apomorphine response was rapid (5–10 min) and durations rarely exceeded 60 min, therefore, the test aporphines were given as pretreatments (90 min–4 h, see Results). All studies used male albino mice, B. K.W. strain; animals were selected from the weight range 20–25 g for climbing and stereotypy experiments, and from the range 35–40 g for stereotaxic surgery to cause circling

behaviour. All behavioural experiments were carried out between 09·00 and 18·00 h in diffusely illuminated rooms maintained at 21 ± 2 °C.

Climbing behaviour was assessed by placing mice in individual cages (20 × 15 × 15 cm) lined with wire mesh as (i) 'the climbing index' which is the percentage of time spent climbing during the 30 min following the first climb and (ii) the 'maximum time' which is the maximum time (in min) spent in a single climb throughout the duration of the apomorphine effect (both parameters are reduced concomitantly by dopamine antagonists except where the interacting drug causes a non-specific sedation or muscular hypotonia when the 'maximum time' is reduced whilst the 'climbing index' is unmodified (see Costall et al 1978). Apomorphine caused a dose-dependent climbing behaviour (0·25–1·5 mg kg^{-1} s.c.): 1 mg kg^{-1} s.c. was selected as a suitable submaximal dose causing intense and consistent climbing for assessment of the effects of potential antagonists.

For measurement of stereotypy the mice were placed in individual Perspex cages (20 × 15 × 15 cm) and the behaviour scored on a simple system of 0—normal motor behaviour indistinguishable from that of vehicle treated animals, 1—repetitive sniffing, 2—periodic biting, 3—continuous biting. These stereotypic effects occurred in the dose range of apomorphine of 1–4 mg kg^{-1} s.c.; 4 mg kg^{-1} s.c. apomorphine was selected for use in the drug interaction studies.

Mice were prepared for circling experiments using standard stereotaxic techniques to place unilateral electrolesions in the right caudate-putamen (1·0 mm anterior to bregma, 2·0 mm lateral and 3·5 mm below the skull surface, 1·5 mA/15 s) (see Costall et al 1979 for details). 14 days after surgery mice were challenged with 0·5 mg kg^{-1} s.c. apomorphine; mice circling ipsilateral to the lesion side less than 6 rev/2 min were excluded from subsequent studies. Ipsilateral circling behaviour was dose-dependent, 0·25–1 mg kg^{-1} s.c. apomorphine causing 2–10 rev/2 min. 0·5 mg kg^{-1} s.c. apomorphine was selected for use in the drug interaction studies.

A further behavioural model utilized the rat (male, Sprague-Dawley, 300 ± 25 g). The procedure was to inject the test aporphines unilaterally into the striatum and determine whether a 'dopamine blockade' had been achieved by subsequent challenge with apomorphine and measurement of any circling induced. Bilateral guide cannulae were chronically implanted, using standard stereotaxic techniques, to allow drug/vehicle injection at the centre of the caudate-putamen complex (Ant. 8·0, Lat. ± 3·0, Vert. + 1·5, De Groot, 1959) (see Costall & Naylor 1976). 14 days after cannulation animals were manually restrained and drug and vehicle injected in a volume of 4 μl (1 μl min^{-1}) into the right and left striata respectively. Any body asymmetry or circling movements resulting from the intracerebral injections were noted, and subsequently any circling behaviour (measured in an open field as rev/2 min) to challenge with 0·5 mg kg^{-1} s.c. apomorphine was measured on the 2nd, 5th, 7th and 14th days following intrastriatal administration.

Biochemical assessments. Experiments were carried out to determine the abilities of the *N*-chloroethyl and *N*-hydroxyethyl aporphine derivatives to inhibit ^{3}H-NPA (Filer et al 1980) binding to striatal tissue. Rats were stunned and the striata dissected out over ice and homogenized (40 vols w/v) in 15 mM Tris-HCl buffer containing 0·01% ascorbic acid and 1 mM Na_2EDTA (pH 7·6 at 25 °C) with a Polytron homogenizer (setting '5' for 10 s). The membranes were precipitated by centrifugation (50 000 g, 10 min) and resuspended in fresh buffer. After the first washing the suspension was preincubated at 37 °C for 10 min. The membranes were then centrifuged and resuspended in two further changes of fresh buffer. Each assay tube contained 5 mg wet weight striatal tissue (equivalent to approximately 275 μg protein, measured by the method of Lowry et al 1951) in a total volume of 1·1 ml. After incubation with 0·125–4·0 nM ^{3}H-NPA (56·2–80·2 Ci m mol^{-1}, New England Nuclear) for 15 min at 25 °C, samples were rapidly filtered under vacuum over Whatman GF/B filters and rinsed rapidly with 2 × 5 ml ice-cold Tris-HCl buffer: the bound radioactivity was measured by liquid scintillation spectrometry (efficiency 43–45%). Specific binding (approximately 4500 d min^{-1} at 2·0 nM) was determined as the difference between ^{3}H-NPA binding in the absence and presence of 10 μM 2-amino-6,7-dihydroxytetrahydro naphthalene (6,7-diOHATN, ADTN) which was added concomitant to the ^{3}H-NPA (for suitability of using 6,7-diOHATN see Quik & Iversen 1978; Fuxe et al 1979; Seeman et al 1979). When using the aporphine derivatives, these or vehicle were added as 5 min preincubations.

The irreversible nature of the receptor inhibition caused by *N*-(2-chloroethyl)- and *N*-(hydroxyethyl)-norapomorphine was assessed by subjecting striatal homogenates to these agents and determining the inhibition of ^{3}H-NPA binding after repeated centrifugation and resuspension ('washing'). The experimental design was to use three tubes each

initially containing 24 ml striatal homogenate (10 mg wet wt tissue ml^{-1}) with addition of (i) *N*-(2-chloroethyl)norapomorphine and (ii) *N*-(hydroxyethyl)norapomorphine, to give final concentrations of 5 μM, or (iii) vehicle for 15 min at 25 °C. Samples were withdrawn, the remaining suspension recentrifuged (50 000 *g*, 10 min), and the pellet resuspended (200 vols w/v above buffer, pH 7·6 at 25 °C). Samples were again taken and the remaining suspension recentrifuged and so forth for a total of 3 'washings'. Each sample was finally incubated with 1·0 nM ^{3}H-NPA at 25 °C for 15 min and filtered as above.

Drugs. (−)*N*-(2-Chloroethyl)norapomorphine. HCl [(−)NCA], (−)*N*-(hydroxyethyl)norapomorphine HCl[(−)NHA], (−)*N*-(2-chloroethyl)norapocodeine HCl [(−)NCC] and 6-[2-bis-(2-chloroethyl)amino] acetyl-11-acetoxy-2-hydroxy-10-methoxy norapomorphine hemihydrate (**I**) (see Fig. 1) were prepared in a minimum quantity of nitrogen-bubbled *NN*-dimethylformamide made up to volume with distilled water (behavioural studies) or Tris-HCl buffer (biochemical studies). Apomorphine HCl (Macfarlan Smith) was prepared in distilled water containing 0·1% sodium metabisulphite.

RESULTS

Inhibition of apomorphine-induced climbing behaviour in the mouse. The maximal climbing response to apomorphine was characterized by a 'climbing index' of approximately 75%. At the test dose of apomorphine, 1 mg kg^{-1} s.c., the climbing index was approximately 60%. This response was reduced to 15–10% 4 h after pretreatment with (−)NCA, 10–20 mg kg^{-1} s.c. A similar antagonism was apparent on the 2nd day following these single administrations of (−)NCA, although responses to apomorphine on the 5th and 7th days approached control values (Fig. 2) (attempts to overcome the inhibition observed 4 h to 2 days after (−)NCA by increasing the dose of apomorphine were made impractical by the development of stereotyped biting at the larger doses which reduced the climbing response per se). 4 h pretreatments with (−)NCC and I or a 90 min pretreatment with (−)NHA (each at 10 mg kg^{-1} s.c.) failed to modify apomorphine climbing (climbing indices of 65·4 ± 8·3; 52·9 ± 8·4 and 67·1 ± 5·1 respectively, control values 59·8 ± 5·9).

Inhibition of apomorphine-induced circling behaviour in the mouse. Apomorphine, 1·0 mg kg^{-1} s.c., caused

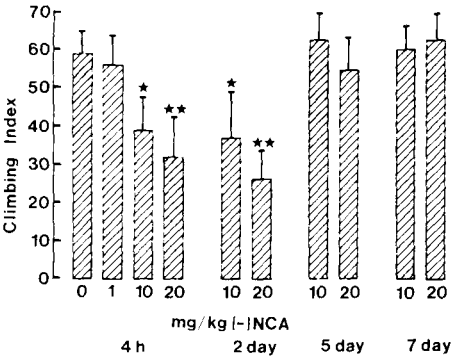

FIG. 2. Effect of (−)NCA, 4 h–7 day after administration in doses of 10 and 20 mg kg^{-1} i.p., on the climbing response to 1 mg kg^{-1} s.c. apomorphine in the mouse. Data are indicated as the 'climbing index.' The 'maximum time' was reduced concomitantly to the climbing index: there were no indications of sedation or muscular hypotonia following (−)NCA administration (see Methods). n = 6, s.e.m.s were < 20%. Reductions in the climbing response caused by (−)NCA significant to * $P < 0.05$, ** $P < 0.02$.

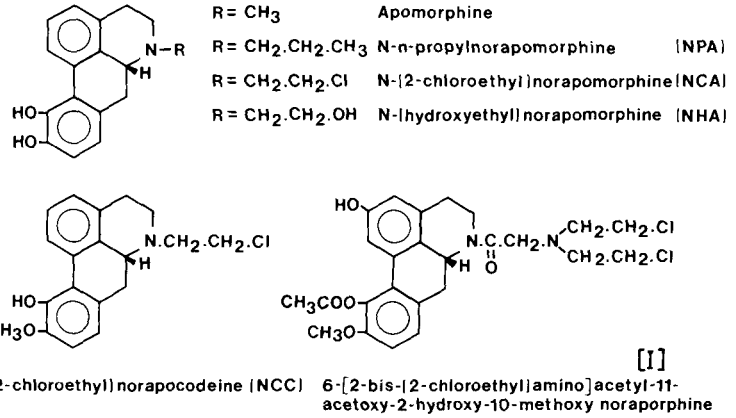

FIG. 1. Structures of aporphines.

a maximum ipsilateral circling response of intensity 10–12 rev/2 min. A submaximal dose of 0·5 mg kg^{-1} s.c. apomorphine selected for the present antagonism studies caused an ipsilateral circling of 6–8 rev/2 min. 2–4 mg kg^{-1} s.c. (−)NCA reduced/abolished this response after 4 h. Further, the reduction was still apparent 2 days following the administration of (−)NCA but recovery of responses towards normal was apparent by the 5th day and complete by the 7th day (Table 1). 4 h pretreatments with (−)NCC and I or a 90 min pretreatment with (−)NHA (each at 10 mg kg^{-1} s.c.) failed to reduce circling.

Induction of circling following unilateral intrastriatal injection in the rat. The unilateral injection of 10 and 40 μg (−)NCA into the caudate-putamen induced tight ipsilateral asymmetry/circling movements within an hour of administration. The resting asymmetry was particularly evident when the animals were disturbed and was also noted 2 and 5 days after the injection of (−)NCA. By the 7th day the ipsilateral asymmetry was variable and was not apparent by the 14th–16th days. The administration of apomorphine (0·5 mg kg^{-1} s.c.) enhanced the ipsilateral asymmetry and precipitated a clear circling behaviour at the 40 μg dose of (−)NCA at 4 h, 2 days and, to a lesser extent, 5 days after its administration (Table 1).

The unilateral intrastriatal injection of up to 40 μg (−)NCC, (−)NHA or I did not cause any consistent asymmetry/circling behaviour either alone or following challenge with apomorphine at any time of testing (no indication of dopamine agonist or antagonist action) (4 h-7 days).

Table 1. Ability of peripherally administered (—) NCA to antagonize circling behaviour induced by 0·5 mg kg^{-1} s.c. apomorphine in mice with unilateral striatal electrolesions, or to cause circling following unilateral intrastriatal injection in rats subsequently challenged with 0·5 mg kg^{-1} s.c. apomorphine. n = 6–8. s.e.m.s < 20%.

	Inhibition of circling in mice		Induction of circling in rats	
Time after admin. (—)NCA	Dose (—)NCA mg kg^{-1}	% reduction circling	Dose (—)NCA unilat. intra-striatal μg/4 μl	Circling rev/2 min
4 h	1·0	0	10·0	2
	2·0	67**	40·0	8·5
	4·0	100**		
2 day	1·0	0	10·0	0
	2·0	14	40·0	8
	4·0	100**		
5 day	2·0	2	10·0	0
	4·0	39*	40·0	3
7 day	2·0	0	10·0	0
	4·0	0	40·0	0

* $P < 0·01$, ** $P < 0·001$.

Failure to antagonize apomorphine-induced stereotyped behaviour in the mouse. Apomorphine, 1–4 mg kg^{-1} s.c., caused stereotyped sniffing and biting behaviour in the mouse which was scored 1–3. At 4 mg kg^{-1} s.c. all mice exhibited a continuous biting behaviour (score 3). 4 h pretreatments with up to 10 mg kg^{-1} s.c. (−)NCA, (−)NCC and I or a 90 min pretreatment with (−)NHA failed to consistently modify the stereotypic effect of 4 mg kg^{-1} s.c. apomorphine, all animals exhibited continuous biting of score 3 ($P > 0·05$ between groups).

Effects of test aporphines on the 'specific' binding of ^{3}H-NPA to striatal homogenates. When used in concentrations of 0·125–8·0 nM, and using 10 μM 6,7-diOHATN to assess 'specific binding', ^{3}H-NPA was found by Scatchard analysis to bind to rat striatal membranes with a KD of 0·82 ± 0·06 nM and a Bmax of 192 ± 17 f mol mg^{-1} protein. Saturation of the 'specific binding' sites occurred at approximately 2·0 nM and at 1·0 nM approximately 35% of the total binding was displaceable by 6,7-diOHATN. (It should be noted that the 'specific binding' of ^{3}H-NPA is less than achieved in our previous study due to an alteration of buffer-incubation conditions which facilitate stereospecific ^{3}N-NPA binding (assessed using (+)- and (−)-butaclamol and the displacement of ^{3}H-NPA by cold (−)NPA, Leysen, personal communication; Jenner, personal communication, Costall et al, in preparation). The IC50 values (nM) for the aporphine derivatives to prevent the binding of ^{3}H-NPA (determined as the concentration of drug causing a half-maximal displacement of 1·0 nM ^{3}H-NPA 'specific binding' assessed as approximately 35% of total binding using 6,7-diOHATN) were 1·2 for (−)NPA, 43·0 for (−)NCA, 175·0 for (−)NHA and > 10^4 for both (−)NCC and I.

Effects of 'washing' on the inhibition of ^{3}H-NPA binding by the test aporphines. Incubation of membranes with (−)NCA (5×10^{-6} M) or (−)NHA (5×10^{-6} M) prevented the 'specific binding' of 1·0 nM ^{3}H-NPA. A single washing significantly removed the (−)NHA inhibition whilst repeated washing caused only modest reversal of the antagonism afforded by (−)NCA (Fig. 3).

DISCUSSION

Apomorphine-induced circling and climbing behaviours in the rodent are considered to involve dopamine agonist action on striatal and mesolimbic

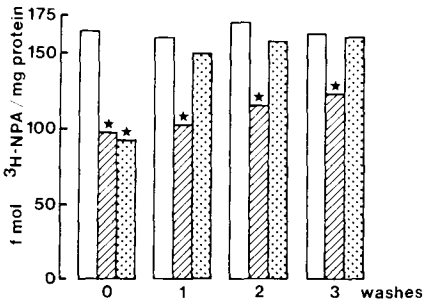

FIG. 3. The effects of 'washing' on the inhibition of ^{3}H-NPA (1·0 nM) binding by (—)NCA (5×10^{-6}, hatched columns) and (—)NHA (5×10^{-6} M, stippled columns). Open columns represent control binding. n = 9–12. s.e.m.s were 4–13%. Inhibition of ^{3}H-NPA binding caused by the test aporphines significant to * $P < 0{\cdot}001$.

dopamine receptors (Ungerstedt 1971; Costall et al 1976; Protais et al 1976; Kelly & Moore 1977; Costall et al 1980b). The antagonism of apomorphine circling and climbing has so far only been achieved by the use of dopamine receptor blocking agents and the present studies extend an inhibitory potential to the aporphine mustards. The peripheral administration of (−)NCA to the mouse reduced apomorphine-induced climbing and inhibited apomorphine-circling, and the unilateral injection of (−)NCA into the striatum of the rat brain caused a circling response to develop following peripheral apomorphine treatment. These results indicate an inhibition of striatal and possibly mesolimbic dopamine function by (−)NCA but the persistence of blockade over a period of days contrasts with the receptor blockade as measured in hours afforded by the classical neuroleptic agents from the phenothiazine and butyrophenone series. The gradual return of the apomorphine responses may reflect a slow desorption of the (−)NCA from the receptor, possibly indicating a long biological half life, or the synthesis of new apomorphine sensitive receptors. If the *N*-chloroethyl grouping in the aporphine structure can facilitate covalent binding to the receptor (as is hypothesized to occur for phenoxybenzamine at the α-noradrenergic receptor, see Introduction), the persistence of the blockade may reflect an irreversible binding, distinct from that of the neuroleptic agents which behave as competitive antagonists. Evidence that (−)NCA can indeed bind to an aporphine sensitive site was obtained from radioligand binding assays. Whilst the most logical selection of ligand for use in the present studies, to directly complement the behavioural data, would be apomorphine, the recent synthesis of tritiated (−)*N*-n-propylnorapomorphine [(−)NPA] (Filer et al 1980), which has superior binding characteristics (Creese et al 1979; Titeler & Seeman 1979), prompted the use of this agent. Using tritiated (−)NPA of very high specific activity, (−)NCA was shown to prevent the 'specific binding' of (−)NPA to rat striatal homogenates and, furthermore, the receptor blockade could not be readily overcome by repeated washing of the membranes.

If the irreversible binding of (−)NCA does indeed involve a covalent linkage to the receptor, the presence of the halogen is a key determinant, and such a binding would not be expected if the halogen were replaced by other groups. (−)NHA was therefore used as a 'control' agent in which the chloro group is replaced by a hydroxyl function. The most important conclusion from the use of this agent is that whilst the affinity of the aporphine for the receptor is maintained, the binding is easily displaced by a single washing. Such facile binding by (−)NHA might perhaps explain the ineffectiveness of (−)NHA to inhibit the apomorphine-induced behavioural changes.

Within the aporphine series optimal dopamine *agonist* action has been associated with the presence of two hydroxyl groups in the 10 and 11 positions (Pinder et al 1971; Neumeyer et al 1977). For example, the substitution of a methoxy group in position 10 in the apomorphine molecule, to form apocodeine, reduces dopamine agonist potential (Lal et al 1972). The importance of a catechol function for effective/maximal binding to the receptor was further emphasized by the present study in which (−)*N*-(2-chloroethyl)apocodeine[(−)NCC] failed to inhibit the behavioural effects of apomorphine in the rat and mouse and was ineffective to prevent ^{3}H-NPA binding. Finally, we assessed the actions of an aporphine mustard with a dichloroethyl substitution. This compound was inactive behaviourally and had no ability to inhibit ^{3}H-NPA binding: the structure included a methoxy substitution in the 10 position which could be expected to reduce binding, a hydroxyl substitution or group in the 2 position and an acetoxy group in the 11 position which is probably hydrolysed. It would be interesting to assess the actions of a similar compound having dichloroethyl substitution but hydroxyl functions in positions 10 and 11.

In summary, we have shown that *N*-chloroethylation in the aporphine series can abolish dopamine agonist action and confer dopamine antagonist potential as assessed behaviourally (antagonism of

apomorphine climbing and circling) and biochemically (^{3}H-NPA binding assay). The binding of (−)NCA to the receptor-indicates an extremely persistent receptor blockade. It was an important observation that apomorphine-induced stereotyped behaviour was not consistently reduced by (−)NCA treatment. The possibility that (−)NCA may irreversibly inactivate some aporphine (dopamine? neuroleptic?) sensitive sites and not others suggests a useful role for this agent in the continuing analysis of dopamine agonist/antagonist action.

Acknowledgements

This work was supported by grants from the Medical Research Council and The Wellcome Trust (University of Bradford) from the National Institutes of Health and the National Cancer Institute (Northeastern University).

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