Psychological Medicine, 1993, **23**, 605–612.

The effect of the dopamine agonist, apomorphine, on regional cerebral blood flow in normal volunteers

P. M. GRASBY,[1] K. J. FRISTON, C. J. BENCH, P. J. COWEN, C. D. FRITH, P. F. LIDDLE, R. S. J. FRACKOWIAK AND R. J. DOLAN

From the MRC Cyclotron Unit, Hammersmith Hospital; Academic Department of Psychiatry, Royal Free Hospital and School of Medicine; National Hospital for Neurology and Neurosurgery; Department of Psychology, University College, London; and MRC Clinical Pharmacology Unit, Littlemore Hospital, Oxford

SYNOPSIS Apomorphine, a non-selective dopamine agonist, has been used as a pharmacological probe for investigating central dopaminergic neurotransmission in psychiatric illness. In this study repeated measurements of regional cerebral blood flow (rCBF) were made in normal volunteers before, and after, the administration of apomorphine (5 or 10 μg/kg), or placebo. The difference in rCBF, before and after drug (apomorphine *versus* placebo), was used to identify brain areas affected by apomorphine. Compared to placebo, both doses of apomorphine increased blood flow in the anterior cingulate cortex. Apomorphine 10 μg/kg also increased prefrontal rCBF (right > left). No decreases in rCBF were noted following either dose of apomorphine. Apomorphine-induced increases of anterior cingulate blood flow might serve as an *in vivo* index of central dopamine function. Such an approach would complement established neuroendocrine challenge paradigms for investigating central dopamine neurotransmission in psychiatric illness.

INTRODUCTION

Apomorphine is a non-selective dopamine agonist with central and peripheral actions (Anden *et al.* 1967; Corsini *et al.* 1981; Creese, 1987). It has been extensively used as a pharmacological probe of dopaminergic systems in both normal volunteers and psychiatric patients (Checkley, 1980; Meltzer *et al.* 1984). In neuroendocrine challenge paradigms apomorphine-induced increases in plasma growth hormone are used as an index of central dopamine receptor function (Checkley, 1980; Lal, 1987). Recently, an enhanced growth hormone response to apomorphine has been reported to be predictive of women at high risk of affective psychosis after childbirth (Wieck *et al.* 1991).

Despite considerable experimental data on apomorphine's central effects in animals, little is known about the brain areas targeted, functionally, by apomorphine in humans. The use of positron emission tomography (PET) to measure drug-induced changes in regional cerebral blood flow (rCBF) is potentially a powerful approach to determine brain systems affected by centrally active drugs. Regional cerebral blood flow measurement is, under most circumstances, a valid index of neuronal activity *in vivo* and, in addition, is sensitive to physiological/behavioural challenges (McCulloch, 1982; Raichle, 1987; Posner *et al.* 1988).

Using positron emission tomography (PET) we report the effects on rCBF of single subcutaneous doses of apomorphine (5 and 10 μg/kg) in normal volunteers. Our aims were to determine: (1) the brain areas altered by apomorphine administration, as indexed by changes in rCBF; and (2) whether the pattern of rCBF change was consistent with the known distribution of central ascending dopaminergic projections and receptors.

METHOD

Subjects

Eighteen right-handed male volunteers (age range 25–36 years) took part in the study which was approved by the Hammersmith Hospital Ethics Committee and the Advisory Committee

[1] Address for correspondence: Dr P. M. Grasby, MRC Cyclotron Unit, Hammersmith Hospital, Du Cane Road, London W12 0HS.

on the Administration of Radioactive Substances (ARSAC) UK.

Drug administration

Each subject underwent six PET measurements of rCBF over an 80 min period. Two measurements of rCBF were undertaken before ($t = -12$, -2 min), and four measurements after ($t = +15$, $+25$, $+45$ and $+55$ min) subcutaneous apomorphine 5, 10 μg/kg or placebo (water for injections). Scan times post apomorphine were chosen on the basis of apomorphine kinetics and the induction of centrally mediated neuroendocrine responses. Time to peak plasma concentration following subcutaneous apomorphine is approximately 8 min with an estimated elimination half-life of approximately 34 min (Gancher *et al.* 1989). Increases of plasma growth hormone begin approximately 15 min following apomorphine 5 μg/kg injection subcutaneously and reach a maximum at approximately 60 min (Costain *et al.* 1982). Subjects were blind to the drug administered. Twelve subjects received apomorphine, six subjects received placebo.

Experimental design

Subjects performed memory tasks during PET scanning. Such standardization of behavioural state may allow for a reduction in intra- and inter-subject variability in rCBF (Duara *et al.* 1987). The behavioural state used for this study was a subspan memory task performed during the 1st, 3rd and 5th scan. A memory task was chosen as the reported experiment formed part of a larger study investigating interactions between monoaminergic drugs and memory processes (Friston *et al.* 1992). Subjects were asked to remember and immediately recall a series of five-word lists presented auditorily. Nine five-word lists were presented over the two minutes of the PET acquisition scan. Words were presented at the rate of one word every two seconds. Words were high frequency, concrete, imageable and were taken from the Oxford Psycholinguistic Data Base (Quinlan, 1992). In this paper the effect of apomorphine on rCBF under the subspan task alone is reported. A more complex memory task was performed during the 2nd, 4th and 6th scans; the effects of this task and apomorphine-memory task interactions on rCBF will be reported separately (see Friston *et al.* 1992 for a preliminary report). Apomorphine or placebo was given after the 2nd scan. Subjects' eyes were closed throughout scanning.

PET scanning

Scans were obtained using a CTI model 931-08/12 PET scanner (CTI, Knoxville, TN, USA) (Spinks *et al.* 1988). Scans were reconstructed using a Hanning filter with a cut-off frequency of 0·5 giving a transaxial resolution of 8·5 mm full width at half maximum and an axial resolution of 6·75 mm for each of 15 transverse planes with a resulting total field of view of 10·13 cm in this direction. To index rCBF, subjects inhaled trace amounts of $C^{15}O_2$, mixed with air, at a concentration of 6 MBq/ml and a flow rate of 500 ml/min through a disposable oxygen face mask for a period of 2 min. Two PET scans were collected over a period of 2·5 min beginning 0·5 min before the inhalation of $C^{15}O_2$ (background scan duration 0·5 min, second scan duration 2·0 min) (adapted from Lammertsma *et al.* 1990). In this study, the integrated counts per pixel for the 2 minute build-up phase of radioactivity in the brain during $C^{15}O_2$ inhalation were used as an index of rCBF (Fox & Mintun, 1989).

Measurement of plasma growth hormone

Apomorphine-induced increases in plasma growth hormone were determined from samples obtained from blood drawn from an in-dwelling venous cannula ($t = -20$, 0, 30 and 60 min post-apomorphine/placebo). Plasma growth hormone was measured by radioimmunoassay as previously described (Cowen *et al.* 1985).

Measurement of side effects of apomorphine administration

Stress and arousal were assessed on three occasions ($t = -15$ min pre-apomorphine/placebo, $+30$ and $+60$ min, post-apomorphine/placebo) on a 24-item questionnaire (Mackay *et al.* 1978). In addition, subjects rated nausea, light-headedness and drowsiness on visual analogue scales.

Data analysis

Each reconstructed rCBF scan consisting of 15 primary transverse planes was interpolated to 43 planes to render the voxels approximately cubic.

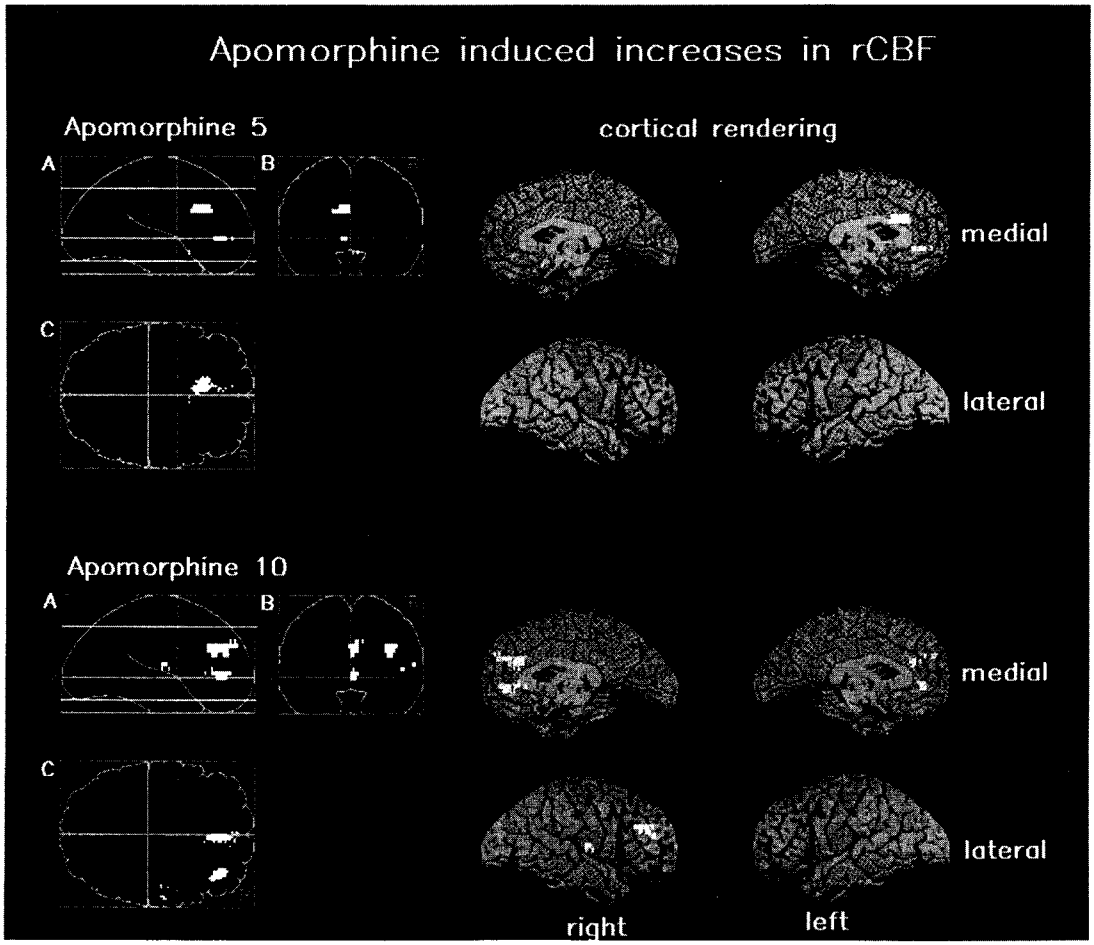

FIG. 1. Location of increases in rCBF following apomorphine (10 and 5 μg/kg) compared to placebo.

Upper left images: the spatial distribution of significant voxels at $P < 0{\cdot}001$ for apomorphine (5 μg/kg)-induced increases in rCBF, compared to placebo. Images are shown as intergrated projections through sagittal (A), coronal (B) and transverse (C) views of the brain. R = right. The axial extent of the data set is indicated by thick lines in the sagittal (A) view. Upper right: to aid interpretation of the areas of activation significant voxels are rendered onto medical and lateral views of each hemisphere.

Lower left images: the spatial distribution voxels at $P < 0{\cdot}001$ for apomorphine (10 μg/kg)-induced increases in rCBF compared to placebo. Images are shown as integrated projections through sagittal (A), coronal (B) and transverse (C) views of the brain. R = right. The axial extent of the data set is indicated by thick lines in the sagittal (A) view. Lower right: to aid interpretation of the areas of activation significant voxels are rendered onto medical and lateral views of each hemisphere.

The data were then transformed into a standard stereotactic space (Friston *et al.* 1989, 1991*a*). Such transformation of the data allows for pixel by pixel averaging of data across subjects. In the standard space 1 voxel represents $2 \times 2 \times 4$ mm in the x, y and z dimensions, respectively, allowing direct cross reference to the anatomical features in the standard stereotactic atlas (Talairach & Tournoux, 1988). A Gaussian filter (20 mm FWHM) was applied to smooth each image to account for inter-subject differences in gyral and functional anatomy and to suppress high frequency noise in the images.

Differences in global activity within and between subjects were removed by analysis of covariance (Wildt & Ahtola, 1978) on a pixel by pixel basis with global counts as covariate and regional activity across subjects for each task as treatment. This procedure was undertaken as inter- and intra-subject differences in global CBF may reduce the likelihood of detecting alterations in rCBF following physiological stimulation (Friston *et al.* 1990). For each pixel, in stereotactic space, the analysis of covariance generated 6 condition-specific (i.e. scans 1–6) mean rCBF equivalent values (normalized to 50 ml/dl/min) and an associated error variance. This error variance was computed independently for the placebo and apomorphine 5 and 10 μg/kg groups using a completely randomized block design ANCOVA. The changes of interest were rCBF changes attributable to apomorphine that were statistically greater than those induced by placebo. This represents an interaction (pre-drug *v.* post-drug × placebo *v.* apomorphine). This interaction term was computed using the t statistic, with the appropriate contrasts (Hand & Taylor, 1991) and adjusted error variance. The resulting set of t values constitutes a statistical parametric map (SPM(t)) (Friston *et al.* 1991*b*). With so many comparisons being made, many t values will reach conventional levels of significance by chance. Therefore, the 'omnibus' significance of the SPMs was assessed, using the χ^2 statistic, by comparing the expected and observed number of t values which exceeded a threshold of $P < 0{\cdot}001$. If this statistic was significant (for a given contrast) the location of all pixels with a t value corresponding to $P < 0{\cdot}001$ was used to define the profile of apomorphine-induced rCBF changes compared to placebo. The results presented are rCBF data from the first pre-drug scan (scan 1) compared to post-drug scans (3 + 5), apomorphine 5 or 10 μg/kg compared to placebo. Because of the smoothing filter used (see above) the final individual values for rCBF at any one pixel represent blood flow in a weighted spherical domain of about 20 mm diameter.

Image analysis was performed using SPM software (MRC Cyclotron Unit, London, UK) on a SPARC 1 workstation (Sun Microsystems Inc., Surrey, UK) using an interactive image analysis software package (ANALYZE), Biodynamic Research Unit, Mayo Clinic, USA). Calculations and image matrix manipulations were performed in PRO MATLAB (Mathworks Inc., New York).

RESULTS

Apomorphine-induced changes in rCBF represent relative increases or decreases compared to placebo. It should be noted that increases and decreases of rCBF may also have occurred outside the axial field of view of the scanner (see Fig. 1).

Observed and expected distribution of t statistic for post-drug (scans 3 + 5) *versus* pre-drug (scan 1) comparisons

Significant differences in the observed and expected distribution of the t statistic (at the threshold of $P < 0{\cdot}001$) for apomorphine (10 μg/kg)-induced increases in rCBF compared to placebo were observed (χ^2 40·1, df 1, $P < 0{\cdot}001$). Using the χ^2 test there was no significance for apomorphine (10 μg/kg)-induced decreases ($\chi^2 = 0$, df 1). Apomorphine (5 μg/kg)-induced increases failed to reach significance at the threshold of $P < 0{\cdot}001$ but were significant at $P < 0{\cdot}01$ ($\chi^2 = 7{\cdot}10$, df 1). Apomorphine (5 μg/kg)-induced decreases were not significant ($\chi^2 = 0$, df 1).

Sites of apomorphine-induced increases of regional cerebral blood flow

Two foci of increased regional cerebral blood flow were observed in the anterior cingulate cortex (2, 40, 4 mm, and 2, 34, 24 mm in Talairach and Tournoux coordinates in the x, y and z plane respectively) following apomorphine 10 μg/kg (Table 1, Fig. 1, Fig. 2). Increased

Table 1. *Coordinates of maximal significant increase in rCBF following apomorphine 10 μg/kg compared to placebo*

	Coordinates (x, y, z)			Apomorphine rCBF change	Placebo rCBF change
Anterior cingulate	2	40	4		
Scan 3–1				2·73 ± 1·86	−0·74 ± 1·28
Scan 5–1				1·97 ± 1·39	−0·38 ± 1·72
Anterior cingulate	2	34	24		
Scan 3–1				2·63 ± 2·02	−1·03 ± 0·80
Scan 5–1				1·91 ± 1·74	−0·88 ± 0·87
Right prefrontal	34	36	28		
Scan 3–1				1·95 ± 0·85	−0·79 ± 1·12
Scan 5–1				1·83 ± 1·24	−1·64 ± 1·04

Stereotactic coordinates of maximal increases in rCBF following apomorphine 10 μg/kg and placebo. Coordinates are given in *x*, *y*, and *z* coordinates in mm, from the atlas of Talairach & Tournoux (1988). Values refer to change in rCBF equivalents (post-drug–pre-drug) from spherical regions of diameter 20 mm centred at the coordinates shown. Results in rCBF equivalents, ml/dl/min, mean ± S.D.

rCBF was also seen in the right prefrontal cortex following apomorphine (10 μg/kg).

For apomorphine (5 μg/kg) a similar pattern of anterior cingulate increases in rCBF was noted (−4, 42, 0 mm and −8, 22, 24 mm in Talairach and Tournoux coordinates in the *x*, *y* and *z* plane respectively) (see Fig. 1) although the χ^2 test for this comparison failed to achieve significance at the threshold of $P < 0{\cdot}001$.

Plasma growth hormone following apomorphine (5 and 10 μg/kg)

Compared to placebo, plasma growth hormone increased following apomorphine administration at 5 and 10 μg/kg. This increase was statistically significant for the 10 μg/kg dose (growth hormone; post-drug at 60 min – pre-drug; apomorphine 10 μg/kg 69 ± 29* mIU/l, apomorphine 5 μg/kg 24 ± 32 mIU/l and placebo 2 ± 3 mIU/l, $*P < 0{\cdot}01$ Student's *t* test unpaired).

Memory performance, stress, arousal and side effects of apomorphine administration

Memory performance in the five-word-list memory task was assessed as the total percentage of words correctly recalled during each scan. Both doses of apomorphine had no effect on the percentage of words correctly recalled (apomorphine 10 μg/kg = 98·5, 98·7, 98·0% and apomorphine 5 μg/kg = 98·0, 98·0 and 100%, means for scans 1, 3 and 5 respectively). Measures of stress decreased during the time of the PET study in both apomorphine 5 μg/kg, 10 μg/kg and placebo treated groups. However, arousal increased in the apomorphine 10 μg/kg group (apomorphine 10 μg/kg; stress 16 ± 5 to 12 ± 2, arousal −3 ± 4 to 4 ± 9, apomorphine 5 μg/kg; stress 17 ± 2 to 13 ± 1, arousal −1 ± 2 to −6 ± 4, placebo group; stress 19 ± 2 to 14 ± 2, arousal −1 ± 2 to −7 ± 3, means ± S.D.). Transient and mild nausea was noted by 3 subjects following apomorphine 10 μg/kg (data not shown).

DISCUSSION

A remarkably similar profile of apomorphine-induced increases of rCBF in the anterior cingulate was observed in both the apomorphine 5 μg/kg and 10 μg/kg treated groups (Fig. 1). The foci of these anterior cingulate activations differed by a maximum of 10, 12 and 4 mm only in the *x*, *y* and *z* planes for the two doses of apomorphine and therefore are unlikely to reflect real differences in the sites of activation between doses. In keeping with the drug's rapid onset and short duration of action (Gancher *et al.* 1989) these increases were greater at the first post-apomorphine 10 μg/kg scan ($t = 15$ min) than the second ($t = +45$ min) (see Table 1 and Fig. 2). Apomorphine-induced increases of rCBF were also seen in right prefrontal cortex at the 10 μg/kg dose (Fig. 1) and the left prefrontal cortex but only at a lower threshold of $P < 0{\cdot}01$ (data not shown). The similarity in the location of rCBF increases in the anterior cingulate with both doses of apomorphine is strong evidence for a significant biological effect. It also suggests that non-specific side effects (transient nausea, increased arousal), seen following apomorphine 10 but not 5 μg/kg, are unlikely to be a sufficient explanation for the changes in rCBF.

The apomorphine-induced increases of rCBF in this study are in broad agreement with the reported stimulatory effects of dopamine agonists on cerebral blood flow (CBF) in animals and man. In man, the dopamine agonists apomorphine, piribedil, bromocriptine and the dopamine precursor L-DOPA all increase CBF (Guell *et al.* 1982; Bes *et al.* 1983; Leenders *et al.* 1985; Sabatini *et al.* 1991). In the anaesthetized baboon apomorphine (0·02–0·5 mg/kg) also

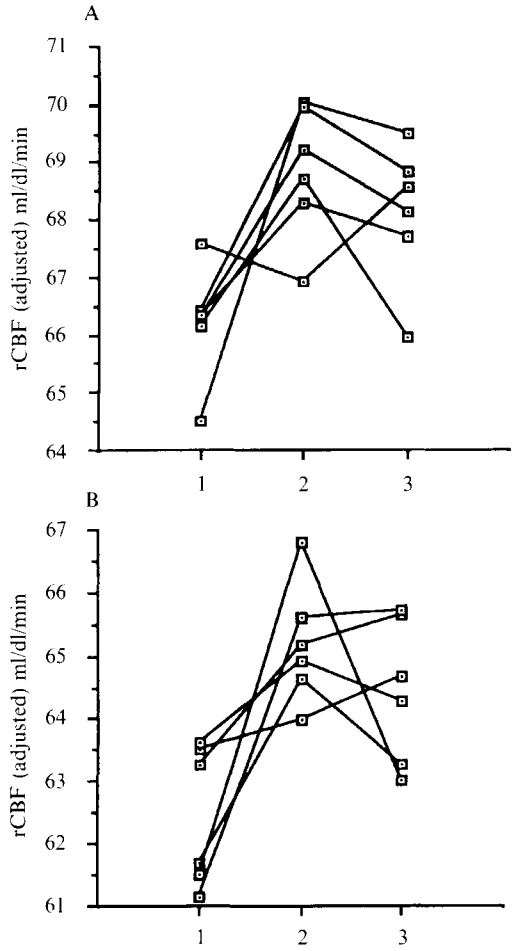

FIG. 2. rCBF increases in the anterior cingulate following apomorphine (10 μg/kg).

Values on ordinate are cerebral blood flow equivalents (ml/dl/min) for individual subjects, normalized to a global blood flow of 50 ml/dl/min, in the anterior cingulate at the two foci of maximal change in rCBF (see Table 1). A. Anterior cingulate at coordinates 2, 34, 24 (mm in *x*, *y* and *z* planes respectively). B. Anterior cingulate at Talairach and Tournoux coordinates 2, 40, 4 (mm in *x*, *y* and *z* planes respectively). ⊡, Individual values for rCBF. The abscissa refers to PET scan sequence: 1, first scan; 2, third scan; 3, fifth scan. Apomorphine was given between points 1 and 2 on the abscissa.

increases CBF (McCulloch & Murray-Harper, 1977). In agreement with our results in some human studies a selective increase in prefrontal rCBF has been noted (Bes *et al.* 1983; Daniel *et al.* 1991). In addition, a relative increase in glucose metabolism in frontal areas has been reported by Cleghorn *et al.* (1991) following apomorphine. In the single tomographic slice examined no anterior cingulate changes were noted (Cleghorn *et al.* 1991).

Despite agreement on the direction of the expected change in CBF, the mechanism of dopamine agonist induced changes in CBF is contentious (see McCulloch *et al.* 1982; Leenders *et al.* 1985). Either of two mechanisms might account for the observed effects; a direct vasodilatory effect of apomorphine on cerebral blood vessels or an effect of apomorphine on neuronal firing, with consequent changes in glucose metabolism and rCBF. This issue is unresolved at present. For example, in Parkinsonian patients apomorphine (0·3 mg s.c.) increased global CBF but this effect was blocked by the peripheral dopamine receptor blocker domperidone (20 mg t.d.s. for 48 h), suggesting a primary vasodilatatory effect of apomorphine

(Sabatini *et al.* 1991). In contrast, the increase in CBF in normal volunteers following the dopamine agonist piribedil was not blocked by domperidone (30 mg 20 min before piribedil) (Guell *et al.* 1982) suggesting a direct metabolic effect. Despite the evidence for dopamine receptors in the cerebral vasculature and the vasodilatory effects of dopamine agonists on cerebral vessels *in vitro* and *in vivo* (Toda, 1976; Edvinsson *et al.* 1978, 1985), there is strong evidence from studies in the conscious rat and the anaesthetized baboon that apomorphine induced changes in cerebral blood flow are secondary to changes in cerebral metabolism (McCulloch & Murray-Harper, 1976; McCulloch *et al.* 1982). In support of a direct effect of apomorphine on neuronal firing, Cleghorn (1991) has recently reported increased posterior frontal metabolism in normal volunteers following apomorphine 10 μg/kg. The discrete regional location of apomorphine-induced increases in rCBF in this study would also favour an explanation via changes in neuronal activity.

Apomorphine stimulates dopamine autoreceptors located on cell bodies or dendrites of dopaminergic neurones but also acts on dopaminergic receptors post synaptic to dopamine neurones (Aghajanian & Bunney, 1977). Either or both sites might be the pharmacological site of action of apomorphine at which the effects on rCBF are mediated. If a direct post-synaptic effect on dopamine receptors in the anterior cingulate is postulated then D_1 receptor stimulation would seem more likely as dopamine D_1 receptors are in higher concentration than dopamine D_2 receptors in cortical areas (Camps *et al.* 1989; Cortes *et al.* 1989). If a direct action on pre-synaptic dopamine autoreceptors is postulated then rCBF changes might be manifest in areas of dense dopaminergic terminal innervation. Unlike the restricted dopaminergic innervation of the rat cortex, in man, most cortical areas are innervated. However, innervation is most dense in the anterior cingulate and motor cortex where dopaminergic projections are to all cortical layers (Berger *et al.* 1991). Whatever the pharmacological site of action of apomorphine in this study, equivalent studies with dopaminergic agonists in animals would suggest that these effects will best be understood in relation to neuroanatomical circuits (McCulloch, 1982; Soncrant *et al.* 1986), of which mesocortical dopaminergic projections are likely to be an important factor.

No striatal activations were noted following either dose of apomorphine. Interestingly, Cleghorn *et al.* (1991) also reported no changes in striatal activity, indexed by glucose consumption, following apomorphine administration in normal volunteers. Mismatches between drug effects and receptor distributions/terminal innervation patterns are clearly described in the animal functional imaging field (McCulloch, 1982). In addition, putative physiological differences between mesostriatal and mesoneocortical dopaminergic systems (De Keyser *et al.* 1990) might account for the differential effects of apomorphine in frontal and striatal areas.

Subjects were studied under the condition of five-word-list learning. Memory task induced activations of neuronal circuits may therefore have masked apomorphine effects in certain brain areas. However, any baseline condition, even a 'resting state', is likely to be associated with activations in distributed networks (e.g. attentional systems). Therefore, drug effects will always be manifest in the context of the integrated functioning of activated neuronal systems. As apomorphine did not affect performance in the five-word-list memory task apomorphine's effects are unlikely to represent an alteration in the magnitude or pattern of memory task activation pre-drug *versus* post-drug.

Further pharmacological characterization with dopamine antagonists is needed to provide a conclusive pharmacological interpretation of our results. Despite this limitation, the results suggest that mapping of central drug effects with PET with serve as an extension to the more established neuroendrocine challenge paradigms for investigating central neurotransmission in psychiatric illness. Thus, while apomorphine-induced increases in plasma growth hormone reflect dopaminergic receptor sensitivity in the hypothalamus (Checkley, 1980), clearly other cortical and limbic structures are more likely candidates for dopaminergic functional abnormalities in psychiatric illness. Apomorphine-induced changes in cingulate rCBF may provide a direct index of central dopaminergic function in a brain area not currently accessible with neuroendocrine challenges.

REFERENCES

Aghajanian, G. K. & Bunnet, B. S. (1977). Dopamine 'auto-receptors'. Pharmacological characterization by micro iontophoretic single cell recording studies. *Naunyn-Schmiedeberg's Archives of Pharmacology* **297**, 1–7.

Anden, N., Rubensen, A., Fuxe, K. & Hokfelt, T. (1967). Evidence for dopamine stimulation by apomorphine. *Journal of Pharmacy and Pharmacology* **19**, 627–628.

Berger, B., Gaspar, P. & Verney, C. (1991). Dopaminergic innervation of the cerebral cortex: unexpected differences between rodents and primates. *Trends in the Neurosciences* **14**, 21–26.

Bes, A., Guell, A., Fabre, N., Arne-Bes, M. C. & Geraud, G. (1983). Effects of dopaminergic agonists (piribedil and bromocriptine) on cerebral blood flow in Parkinsonism. *Journal of Cerebral Blood Flow and Metabolism* **3**, suppl S490–S491.

Camps, M., Cortes, R., Gueye, B., Probst, A. & Palacious, J. M. (1989). Dopamine receptors in human brain: autoradiographic distribution of D2 sites. *Neuroscience* **28**, 275–290.

Checkley, S. A. (1980) Neuroendocrine tests of monoamine function in man: a review of basic theory and its application to the study of depressive illness. *Psychological Medicine* **10**, 35–53.

Cleghorn, J. M., Szechtman, H., Garnett, E. S., Nahmias, C., Brown, G. M., Kaplan, R. D., Szechtman, B. & Franco, S. (1991) Apomorphine effects on brain metabolism in neuroleptic-naive schizophrenic patients. *Psychiatry Research Neuroimaging* **40**, 135–153.

Corsini, G. U., Piccardi, M. P., Bocchetta, F., Bernardi, F. & Del Zompo, M. (1981). Behavioural effects of apomorphine in man: dopamine receptor implications. In *Apomorphine and Other Dopaminomimetics, Vol. 2: Clinical Pharmacology* (ed. G. U. Corsini and G. L. Gessa), pp. 13–24, Raven Press: New York.

Cortes, R., Gueye, B., Pazos, A., Probst, A. & Palacious, J. M. (1989). Dopamine receptors in human brain: autoradiographic distribution of D1 sites. *Neuroscience* **28**, 263–273.

Costain, D. W., Cowen, P. J., Gelder, M. G. & Grahame-Smith, D. G. (1982). Electroconvulsive therapy and the brain: evidence for increased dopamine mediated responses. *Lancet* ii, 400–404.

Cowen, P. J., Gadhui, H., Gosden, B. & Kolakowska, T. (1985). Responses of prolactin and growth hormone to L-tryptophan infusion: effects in normal subjects and schizophrenic patients receiving neuroleptics. *Psychopharmacology* **86**, 164–169.

Creese, I. (1987). Biochemical properties of CNS dopamine receptors. In *Psychopharmacology: The Third Generation of Progress* (ed. H. Y. Meltzer), pp. 258–260. Raven Press: New York.

Daniel, D. G., Berman, K. F. & Weinberger, D. R. (1991). The effect of apomorphine on regional cerebral blood flow in schizophrenia. *Journal of Neuropsychiatry* **1**, 377–384.

De Keyser, J., Herregodts, P. & Ebinger, G. (1990). The meso-neocortical dopamine neuron system. *Neurology* **40**, 1660–1662.

Duara, R., Gross-Glen, K., Barker, W. W., Chang, J. Y., Apicella, A., Lowenstein, D. & Boothe, T. (1987). Behavioural activation and the variability of cerebral metabolic measurements. *Journal of Cerebral Blood Flow and Metabolism* **7**, 266–271.

Edvinsson, L., Harbedo, J.-E., McCulloch, J. & Owman, C. (1978). Effects of dopaminergic agonists and antagonists on isolated cerebral blood vessels. *Acta Physiologica Scandinavica* **105**, 349–359.

Edvinsson, L., McCulloch, J. & Sharkey, J. (1985). Vasomotor responses of cerebral arterioles in situ to putative dopamine receptor agonists. *British Journal of Pharmacology* **85**, 403–410.

Fox, P. T. & Mintun, M. A. (1989). Non-invasive functional brain mapping by change distribution analysis of averaged PET images of $H_2{}^{15}O$ tissue activity. *Journal of Nuclear Medicine* **30**, 141–149.

Friston, K. J., Passingham, R. E., Nutt, J. G., Heather, J. D., Sawle, G. V. & Frackowiak, R. S. J. (1989). Localization in PET images: direct fitting of the intercommissural (AC–PC) line. *Journal of Cerebral Blood Flow and Metabolism* **9**, 690–695.

Friston, K. J., Frith, C. D., Liddle, P. F., Lammertsma, A. A., Dolan, R. J. & Frackowiak, R. S. J. (1990). The relationship between local and global changes in PET scans. *Journal of Cerebral Blood Flow and Metabolism* **10**, 458–466.

Friston, K. J., Frith, C. D., Liddle, P. F. & Frackowiak, R. S. J. (1991*a*). Plastic transformation of PET images. *Journal of Computer Assisted Tomography* **15**, 634–639.

Friston, K. J., Frith, C. D., Liddle, P. F. & Frackowiak, R. S. J. (1991*b*). Comparing functional (PET) images: the assessment of significant change. *Journal of Cerebral Blood Flow and Metabolism* **11**, 690–699.

Friston, K. J., Grasby, P. M., Bench, C., Frith, C. D., Cowen, P. J., Liddle, P. F., Frackowiak, R. S. J. & Dolan, R. J. (1992). Measuring the neuromodulatory effects of drugs in man with positron emission tomography. *Neuroscience Letters* **141**, 106–110.

Gancher, S., Woodward, W., Boucher, B. & Nutt, J. (1989). Peripheral pharmacokinetics of apomorphine in humans. *Annals of Neurology* **26**, 232–238.

Guell, A., Geraud, G., Jauzac, Ph., Victor, G. & Arne-Bes, M. C. (1982). Effects of a dopaminergic agonist (piribedil) on cerebral blood flow in man. *Journal of Cerebral Blood Flow and Metabolism* **2**, 255–257.

Hand, D. J. & Taylor, C. C. (1991). *Multivariate Analysis of Variance and Repeated measures* pp. 9–44. Chapman and Hall: London.

Lal, S. (1987). Growth hormone response and schizophrenia. In *Psychopharmacology: The Third Generation of Progress* (ed. H. Y. Meltzer), pp. 809–818. Raven Press: New York.

Lammertsma, A. A., Cunningham, V. J., Deiber, M. P., Heather, J. D., Bloomfield, P. M., Nutt, J. G., Frackowiak, R. S. J. & Jones, T. (1990). Combination of dynamic and integral methods for generating reproducible function CBF images. *Journal of Cerebral Blood Flow and Metabolism* **10**, 675–686.

Leendeers, K. L., Wolfson, L., Gibbs, J. M., Wise, R. J. S., Causon, R., Jones, T. & Legg, N. J. (1985). The effects of L-dopa on regional cerebral blood flow and oxygen metabolism in patients with Parkinson's disease. *Brain* **108**, 171–191.

Mackay, C., Cox, T., Burrows, G. & Lazzerini, T. (1978). An inventory for the measurement of self-reported stress and arousal. *British Journal of Social and Clinical Psychology* **17**, 283–284.

McCulloch, J. (1982). Mapping functional alterations in the CNS with [14C]-deoxyglucose. In *Handbook of Psychopharmacology* (ed. L. I. Iversen, S. D. Iverson and S. H. Snyder), pp. 321–410. Plenum: New York.

McCulloch, J. & Murray-Harper, A. (1977). Cerebral circulation: effect of stimulation and blockade of dopamine receptors. *American Journal of Physiology* **233**, H222–H227.

McCulloch, J., Kelly, P. A. T. & Ford, I. (1982). Effect of apomorphine on the relationship between local cerebral glucose utilization and local blood flow (with an appendix on its statistical analysis). *Journal of Cerebral Blood Flow and Metabolism* **2**, 487–499.

Meltzer, H. Y., Kolakowska, T., Fang, V. S., Fogg, L., Robertson, A., Lewine, R., Strahilevitz, M. & Busch, D. (1984). Growth hormone and prolactin response to apomorphine in schizophrenia and the major affective disorders. *Archives of General Psychiatry* **41**, 512–520.

Posner, M. I., Petersen, S. E., Fox, P. T. & Raichle, M. E. (1988). Localization of cognitive operations in the human brain. *Science* **240**, 1627–1631.

Quinlan, P. T. (1992). *The Oxford Psycholinguistic Database*. Oxford University Press: Oxford.

Raichle, M. E. (1987). Circulatory and metabolic correlations of brain function in normal humans. In *Handbook of Physiology. Section 1: The Nervous System. Vol. 5: Higher Functions of the Brain* (ed. F. Plum), pp. 643–674. Oxford University Press; New York.

Sabatini, U., Rascol, O., Celsis, P., Houin, G., Rascol, A. & Marc-Vergnes, J. P. (1991). Subcutaneous apomorphine increases regional cerebral blood flow in parkinsonian patients via peripheral mechanisms. *British Journal of Clinical Pharmacology* **32**, 229–234.

Soncrant, T. T., Pizzolato, G. & Battistin, L. (1986). The use of drugs as probes of cerebral function In *PET and NMR: New Perspectives*

in Neuroimaging and in Clinical Neurochemistry (ed. L. Battistin and F. Gerstenbrand), pp. 131–149. Alan R. Liss: New York.

Spinks, T. J., Jones, T., Gilardi, M. C. & Heather, J. D. (1988). Physical performance of the latest generation of commercial positron scanner. *IEEE Transactions on Nuclear Science* **35**, 721–725.

Talairach, J. & Tournoux, P. (1988). *A Co-Planar Stereotactic Atlas of the Human Brain*. Thieme Verlag: Stuttgart.

Toda, N. (1976). Influence of dopamine and noradrenaline on isolated cerebral arteries of the dog. *British Journal of Pharmacology* **58**, 121–126.

Wieck, A., Kumar, R., Hirst, A. D., Campbell, I. C. & Checkley, S. A. (1991). Increased sensitivity of dopamine receptors and recurrence of affective psychosis after childbirth. *British Medical Journal* **303**, 613–616.

Wildt, A. R. & Ahtola, O. T. (1978). *Analysis of Covariance*. (University papers: quantitative applications in the social sciences Ser. no. 12) Sage Publications: Beverly Hills, CA.