Domperidone treatment in man inhibits the fall in plasma renin activity induced by intravenous γ -L-glutamyl-L-dopa

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1 The dopamine pro-drug γ -L-glutamyl-L-dopa (gludopa) was administered intravenously to six normal subjects at a dose of $12.5 \mu\text{g min}^{-1} \text{kg}^{-1}$, either with or without the dopamine antagonist domperidone. A control was provided by the intravenous infusion of domperidone and saline on a separate occasion.

2 Intravenous gludopa produced a significant natriuresis, whether administered alone or in combination with domperidone.

3 After gludopa infusion, there was a significant fall in plasma renin activity, an effect which was attenuated significantly by concomitant treatment with domperidone.

4 These observations suggest that blockade of renal DA_2 dopamine receptors has little or no effect on gludopa-induced natriuresis, but that at least part of the dopaminergic inhibition of renin release is mediated by renal DA_2 receptors.

Keywords dopamine domperidone plasma renin activity renal haemodynamics natriuresis L-dopa

Introduction

According to the classification of Goldberg and Kohli, peripheral dopamine (DA) receptors are of either DA_1 , or DA_2 subtype (Goldberg & Kohli, 1983). Renal vasodilatation induced by dopamine is mediated by vascular DA_1 receptors, but it is uncertain whether the natriuresis due to this catecholamine results simply from alterations in renal blood flow, or from the stimulation of specific tubular receptors. Dopamine reduces proximal tubular fluid reabsorption (Bello-Reuss *et al.*, 1982), and DA receptors have been demonstrated on rabbit proximal tubule (Felder *et al.*, 1984), suggesting that there are indeed specific tubular receptors for dopamine, although the exact subtype remains uncertain. Dopamine is also known to affect the renin-angiotensin aldosterone system, at the level of both the adrenal gland (Witzgall *et al.*, 1985) and the kidney (Sowers *et al.*, 1982). Dopaminergic inhibition of renin release has been demonstrated recently in animals (Sowers

et al., 1981) and in human subjects (Worth *et al.*, 1985), although again, the receptor subtype is not known.

Since dopaminergic drugs are being developed for use in the treatment of disorders such as heart failure and essential hypertension (Goldberg, 1984), it is of interest to know which DA receptors mediate potentially therapeutic dopamine effects. We, therefore, conducted a study to investigate the effect of the peripheral DA_2 antagonist, domperidone (Laduron & Leyson, 1979; Glock *et al.*, 1982), on the changes in the renal function of normal human subjects produced by the relatively kidney-specific dopamine pro-drug γ -L-glutamyl-L-dopa (gludopa). This dipeptide, when administered intravenously at $12.5 \mu\text{g min}^{-1} \text{kg}^{-1}$ to normal subjects (Worth *et al.*, 1985) resulted in a 250-fold increase in urine free dopamine excretion with only a four-fold rise in plasma DA concentration, and no alteration in pulse or blood pressure. Renal vasodila-

tation, natriuresis and a fall in plasma renin activity (PRA) also occurred. In view of its relative renal specificity, gludopa provides a useful tool for investigating dopamine-induced changes in renal function.

Methods

The protocol for the study was approved by the Ethics Committee of Leeds General Infirmary, and all subjects gave informed consent.

Six normal male subjects, aged 26–32 years, were studied on three occasions, separated by at least 1 week, when they received either gludopa alone, domperidone alone, or the two drugs together.

Gludopa was synthesised by UCB Bioproducts Ltd (Rue Berkendael 68, 1060 Brussels, Belgium) and shown to contain 92% peptide, by thin layer and high performance liquid chromatography, the balance being acetic acid carried over from freeze drying. It was dissolved in 0.9% sodium chloride solution (saline), with 0.05% human albumin as carrier, and made up into 5 ml ampoules containing 100 mg gludopa. Domperidone was obtained from Janssen Pharmaceuticals Ltd, as the intravenous preparation containing domperidone 5 mg ml⁻¹.

No strict dietary control was imposed, but during the day preceding each study, subjects avoided alcohol, caffeine-containing drinks (12 h) and cigarettes (6 h). Sodium intake was not controlled or measured, but in order to reduce the range of values for basal sodium excretion, subjects were asked to avoid foods with a high salt content, for 24 h prior to the study. Thirty minutes before the study, intravenous cannulae were placed in both antecubital fossae, for blood sampling and drug administration. Each study consisted of three 2 h periods: during the first (–2–0 h) and last (2–4 h), saline was administered i.v. at a dose of 0.6 ml kg⁻¹. During the middle period (0–2 h), either gludopa 12.5 µg min⁻¹ kg⁻¹ in saline 0.6 ml kg⁻¹, or saline 0.6 ml kg⁻¹ was infused intravenously: immediately before this infusion, a bolus i.v. injection (2 ml) of either domperidone 10 mg or 5% dextrose was given. In addition to the bolus dose, domperidone 30 mg in 6 ml, or 5% dextrose (6 ml), was infused i.v. during the second and third periods (0–4 h), the rate of infusion of domperidone being 7.5 mg h⁻¹. The drugs were administered in such a way that subjects received, in random order, either gludopa with dextrose, gludopa with domperidone, or saline with domperidone. Every hour, 200 ml of water was taken orally to ensure an adequate urine flow. Urine was collected during

each 2 h period for measurement of volume and sodium concentration. Blood was taken at the end of each period for estimation of plasma renin activity (PRA) and, in four subjects, plasma aldosterone (PA). An i.v. injection of [¹²⁵I] orthoiodohippurate (OIH) 10 µCi, and ⁵¹Cr labelled ethylene diamine tetraacetic acid (EDTA), 30 µCi, was given 30 min into the middle period, for measurement of effective renal plasma flow (ERPF) and glomerular filtration rate (GFR). Multiple blood samples were taken after the injection, and urine collected 90 min later (at time 2 h) for gamma-counting, with an additional voiding 30 min after the injection to ensure accuracy of collection. Blood pressure and pulse rate were measured in duplicate every 15 min using a Dinamapp monitor (Critikon Ltd).

PRA was estimated by radioimmunoassay (Haber *et al.*, 1969) with intra- and inter-assay coefficients of variation (CV) of 6.1% and 7.3% respectively. Plasma aldosterone was also measured by a radioimmunoassay (Diagnostic Products), with an intra-assay CV between duplicate results, of 6%. Urine sodium concentrations were measured by autoanalyser. The cumulative integral method of Harries *et al.* (1972) was used for the measurement of ERPF and GFR, with CVs of 9% and 4% respectively.

The Wilcoxon matched pair signed-rank test was used for assessment of the data on ERPF, GFR, PRA, urine flow and urine electrolyte excretion. The means of individual's blood pressure and pulse rate values over hours 2, 3, 4, 5 and 6 were compared by the Friedman non-parametric two-way analysis of variance.

Results

On administration of gludopa there was an increase in mean urinary sodium excretion (Table 1), from 4.8 ± 0.9 mmol h⁻¹ during the run-in period (–2–0 h) to 7.1 ± 1.0 during the infusion (0–2 h), the increment over baseline being significant when compared to the fall occurring during the control study (*P* < 0.05). The natriuresis induced by gludopa was not affected by simultaneous treatment with domperidone, since the mean urinary sodium excretion on the combination of drugs also arose, from 6.5 ± 1.3 mmol h⁻¹ (–2–0 h) to 8.6 ± 1.5 (0–2 h), which was significant when compared to the changes occurring on domperidone alone (*P* < 0.05). There were no significant changes in urine sodium excretion at 2–4 h with either gludopa alone, or in combination with domperidone, when compared to the control data (domperidone).

Table 1 Mean, urine sodium (U_{Na} V) and potassium (U_K V) excretion, and urine flow, in six normal subjects receiving gludopa, gludopa with domperidone, or domperidone. Values are mean $\pm$ s.e. mean.

	Gludopa			Gludopa and domperidone			Domperidone		
	-2-0	0-2	2-4	-2-0	0-2	2-4†	-2-0	0-2	2-4 h
U_{Na} V	4.8	7.1*	7.3	6.5	8.6*	6.6	5.1	4.0	3.1
(mmol h ⁻¹)	0.9	1.0	1.3	1.3	1.5	0.6	1.2	0.8	0.6
U_K V	4.3	6.6	4.4	5.1	7.8	4.6	5.5	6.7	4.1
(mmol h ⁻¹)	1.1	0.9	0.5	1.0	2.4	1.6	1.0	1.6	0.5
Urine flow	171	300	230	210	279	230	205	236	203
(ml h ⁻¹)	29	8	16	77	37	9	48	21	10

*, $P < 0.05$ for increment over baseline (-2-0) compared to control (domperidone)

† $n = 5$

There was an increase in mean urine flow on all study days (Table 1), and although gludopa, with or without domperidone, appeared to cause a greater diuresis than domperidone alone, there were no significant differences between the treatments. Mean urinary potassium excretion (Table 1) also increased to a similar extent on all forms of treatment.

Gludopa infusion caused mean ERPF to increase by 18% over baseline (Table 2), and gludopa with domperidone resulted in a 7% increase, although neither of these changes was significant. Similarly, mean GFR increased on both gludopa alone and in combination with domperidone, by 17% and 11% over baseline respectively, although as with ERPF, these changes did not reach statistical significance.

Mean PRA fell immediately after gludopa infusion (Figure 1, Table 3) from 2.2 ± 0.3 ng AI h⁻¹ ml⁻¹ (time 0) to 1.5 ± 0.4 (time 2 h), the decrement differing significantly from the rise which occurred on domperidone alone ($P < 0.05$). When domperidone was given with gludopa there was a small but non-significant fall in mean PRA, from 2.1 ± 0.3 to 2.0 ± 0.4 ng AI h⁻¹ ml⁻¹ which was significantly different from the marked

fall in PRA which occurred on gludopa alone ($P < 0.05$).

Mean plasma aldosterone concentration (four subjects) decreased after all treatments (Table 3), with a greater fall at 2 h following gludopa (-41%) than after domperidone (-15%) or gludopa plus domperidone (-9%).

There were no significant changes in mean blood pressure or pulse rate and no adverse effects with any of the treatments. The absence of systemic effects of gludopa confirms our previous observations (Worth *et al.*, 1985).

Discussion

At this dose domperidone did not abolish the natriuretic action of gludopa, suggesting that the major part of this effect is not mediated through DA₂ receptors. Other doses of domperidone were not studied, but animal experiments suggest that the dose used in the present study (0.46–0.61 mg kg⁻¹) is likely to have achieved adequate DA₂ receptor blockade. Although no equivalent human studies have been undertaken, work in the dog indicates that dose-related DA₂ blockade

Table 2 Mean effective renal plasma flow (ERPF), glomerular filtration rate (GFR) and filtration fraction (FF) in six normal subjects receiving gludopa, gludopa with domperidone, or domperidone. Values are mean $\pm$ s.e. mean

	Gludopa	Gludopa and domperidone	Domperidone
ERPF	619	600	559
(ml min ⁻¹)	42	68	58
GFR	123	122	111
(ml min ⁻¹)	8	10	11
FF	0.20	0.21	0.20
	0.01	0.01	0.01

Figure 1 Plasma renin activity (PRA) in six normal subjects, receiving gludopa, gludopa with domperidone or domperidone.

occurs at $0.5\text{--}5.0\ \mu\text{g kg}^{-1}$, with no DA_1 antagonism even at $5\ \text{mg kg}^{-1}$ (Glock *et al.*, 1982). The lack of effect of a DA_2 receptor antagonist on the gludopa-induced natriuresis is consistent with the observation that dopamine-induced natriuresis in the dog is inhibited by the peripheral DA_1 antagonist SCH 23390 (Frederickson *et al.*, 1984). Since an increase in renal sympathetic nerve activity can result in sodium retention, and a reduction in activity, producing a natriuresis (Moss, 1982), inhibition of adrenergic neurones by stimulation of pre-synaptic DA_2 receptors might be proposed as a mechanism for a part of the dopamine-induced natriuresis. The present study, however, indicates that this was not an important effect in our subjects.

In a previous study of gludopa in normal subjects, we demonstrated a significant increase in mean ERPF and GFR (Worth *et al.*, 1985). It is possible that the renal haemodynamic changes

in the present study failed to reach significance because fewer subjects were studied. However, in view of the reported α_1 -adrenoceptor antagonist activity of domperidone (Ennis & Cox 1980), it is also possible that there was a slight renal vasodilatation during the control study, resulting from a reduction in renal sympathetic nerve activity as a result of the action of domperidone itself. Nevertheless, the trend towards an increase in ERPF and GFR on gludopa did not appear to be reduced by concomitant treatment with domperidone, which would be consistent with the known mediation of renal vasodilatation by DA_1 receptors (Goldberg & Kohli, 1983).

In the current study, basal PRA was higher, and sodium excretion lower, than in earlier work (Worth *et al.*, 1985). These differences may simply represent random differences, or may indicate greater activation of the renin-angio-

Table 3 Mean plasma renin activity (PRA) in six normal subjects, and plasma aldosterone (PA) concentrations, in four subjects, receiving gludopa, gludopa with domperidone or domperidone. Values are mean $\pm$ s.e. mean

	Gludopa			Gludopa and domperidone			Domperidone		
	0	2	4	0	2	4	0	2	4 h
PRA	2.2	1.5*	1.9	2.1	2.0	2.2	2.1	2.5	2.6
(ng AI ml ⁻¹ h ⁻¹)	0.3	0.4	0.3	0.3	0.4	0.4	0.3	0.4	0.4
PA	368	218	206	375	343	251	489	415	298
(pmol l ⁻¹)	73	30	30	51	78	31	61	34	42

* $P < 0.05$ for change from baseline (0 h) compared to both other study days.

tensin-aldosterone axis in the present study, which was conducted during unusually warm weather. However, administration of gludopa resulted in a 30% fall in PRA in both studies, and the slight rise in PRA on the control day in the current study (domperidone alone) was similar to the rise occurring with saline alone in the previous work. These observations suggest that the direction and magnitude of PRA changes induced by gludopa are not affected by physiological alterations in the degree of activation of the renin-angiotensin axis. The slight rise in PRA seen with domperidone alone in the present study, and the similar rise observed with saline alone in previous work (Worth *et al.*, 1985), are in agreement with the lack of effect of domperidone on PRA demonstrated by Sowers and co-workers (1982). The attenuation by domperidone of the gludopa-induced fall in PRA, therefore suggests that a part of the effect of gludopa on PRA is mediated by a DA₂ receptor. Our observations on the effect of gludopa in man differ from previous reports on the effect of i.v. dopamine, where doses of 5 µg min⁻¹ kg⁻¹ (Witzgall *et al.*, 1985) or up to 600 µg min⁻¹ (Wilcox *et al.*, 1974) have been shown to increase PRA. It would appear, therefore, that in man, pharmacological doses of dopamine intravenously result in an increase in PRA. Animal studies have shown that PRA rises when high doses of DA are given (Otsuka *et al.*, 1970), or when dopamine is administered to animals with denervated kidneys (Imbs *et al.*, 1975; Holdaas, 1982). *In vitro* studies using dopamine at 10⁻⁵ M concentrations have also demonstrated a dopamine-induced rise in PRA (Quesada *et al.*, 1979; Henry *et al.*, 1977). When the renal nerves are intact, and lower (but nevertheless pharmacological) doses of DA are used, PRA is not altered significantly (Chokshi *et al.*, 1979; Otsuka *et al.*, 1970). Furthermore, if CNS dopamine concentration is increased and

the renal nerves are left intact, there is a fall in PRA (Blair *et al.*, 1977). These findings, and the present observations, could be explained by the existence of a balance, in the intact subject, between dopamine stimulation of PRA release through DA₁ or β₁-adrenoceptors (Vanhees *et al.*, 1985), and dopaminergic inhibition of PRA release through an effect of peripheral DA₂ pre-synaptic, or central, DA receptors. A central dopamine effect cannot be entirely excluded, but is unlikely, since domperidone, which abolished the gludopa-induced fall in PRA, has been shown not to cross the blood-brain-barrier (Laduron & Leysin, 1979), and dopamine itself penetrates the cerebrospinal fluid poorly.

The changes in plasma aldosterone are interesting, but the small number of subjects prevents any firm conclusions being drawn. However, the absence of any rise in mean PA following domperidone is in agreement with the studies of Sowers *et al.* (1982) who found no increase in PA after domperidone administration, in contrast to the sharp rise known to occur following metoclopramide (Carey *et al.*, 1979).

These observations suggest that there is little or no contribution of DA₂ receptors to gludopa-induced renal vasodilatation and natriuresis, but suggest that there is a peripheral dopaminergic inhibition of renin release mediated in part by the DA₂ receptor. Exploitation of this effect may prove valuable in the development of dopamine agonists for the treatment of hypertension and heart failure.

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