Different effects of metoclopramide and domperidone on arginine-vasopressin secretion in man

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This study was performed in order to investigate the dopaminergic mechanism involved in the control of arginine-vasopressin (AVP) secretion in normal men. Plasma AVP concentrations were measured before and after the administration of an i.v. bolus of 10 mg metoclopramide or domperidone to twelve healthy males. Metoclopramide, a cerebral and peripheral antagonist of dopaminergic receptors, significantly stimulated AVP secretion, whereas domperidone, a dopamine antagonist which does not cross the blood–brain barrier, was without effect. These data suggest that metoclopramide stimulates the release of AVP by blocking dopaminergic receptors in structures located inside the blood–brain barrier. Alternatively, it is possible that the stimulation of AVP release induced by metoclopramide does not occur through inhibition of dopamine receptors but rather through interaction with other neuroendocrine pathways.

Keywords metoclopramide domperidone vasopressin

Introduction

The dopamine receptor antagonist metoclopramide, which readily crosses the blood–brain barrier (BBB) (Peringer *et al.*, 1976), stimulates arginine-vasopressin (AVP) secretion in man (Nomura *et al.*, 1984). The mechanism of action of metoclopramide is not well delineated, since it is unknown whether this drug stimulates AVP release by blocking dopaminergic activity directly at the level of the neurohypophysis or via effects on the central nervous system. The dopaminergic system seems to be involved at various levels in the control of AVP secretion. Central dopaminergic neurons terminate in the supraoptic nucleus, in the median eminence and in the neurohypophysis (Fuxe & Hokfelt, 1969; Cuello & Iversen 1973; Parry & Livett, 1973; Zimmerman *et al.*, 1973; Passo *et al.*, 1981). The majority of these systems, constituted by cell bodies and proximal parts of axons, lie inside the BBB, while nerve terminals are located in the median

eminence and neurohypophysis and thus lie outside the BBB (Loizou, 1970; Davson, 1972; Rapaport, 1976). In order to assess whether the effect of metoclopramide is mediated by an action on dopamine receptors within or outside the BBB, the present study evaluated the response of normal men to domperidone, a dopamine antagonist which does not readily cross the BBB (Baudry *et al.*, 1979; Laduron & Leysen, 1979).

Methods

Twelve normal men, 21–36 years old, volunteered for this study. All subjects were within 10% of their ideal body weight and were free from endocrine and metabolic disorders. None of them was taking any drug for at least 2 weeks before the experimental days or was allowed to smoke for 12 h before the tests were started.

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Each subject was submitted to two tests; one consisted in the intravenous injection of a bolus of 10 mg metoclopramide, the other in a similar injection of 10 mg domperidone. Tests were performed in random order with an interval of at least 6 days between tests. A similar protocol was followed in both tests. At 08.30 h on the experimental day, an intravenous catheter was inserted into a forearm vein of subjects fasting and resting in bed within the hospital building from the previous evening. During tests the men remained in the recumbent position; catheters were kept open with a very slow infusion of normal saline. Two basal blood samples were withdrawn at an interval of 15 min; the second sampling was followed by a rapid injection of 10 mg metoclopramide or domperidone. Further blood specimens were collected 15, 30, 45, 60, 90 and 120 min after drug injections. Further experimental tests were performed in six out of the 12 subjects in order to establish the effect of a higher dose of domperidone on AVP secretion. This time, 20 mg domperidone was given. The experimental procedure was the same as previously described. During all tests, blood pressure was monitored before and after metoclopramide and domperidone administration. All blood samples were placed in iced tubes containing EDTA (1 mg ml^{-1}) and aprotinin (100 k iu ml^{-1}) for evaluation of AVP levels and blood osmolality, and into plastic tubes containing K_3EDTA for haematocrit evaluation. Plasma for measurement of AVP concentrations was separated, frozen and stored at -20°C for 3–4 weeks until assayed with a specific radioimmunoassay method (Chiodera *et al.*, 1984b). All samples from the same subject were processed in duplicate and in the same assay. The sensitivity of the assay was about 1.2 pg ml^{-1} . Intra- and inter-assay coefficients of variations were 11% and 12.8%, respectively. Osmolality was determined with an advanced osmometer (Osmette S, Sedas s.r.l.). Haematocrit was measured by

a Drummond microhaematocrit (Drummond Scientific Co, Broomal, Ca.). Statistical analysis was performed using the paired Student's *t*-test. Results are expressed as mean $\pm$ s.e. mean.

Results

Table 1 shows the effect of metoclopramide or domperidone on circulating plasma levels of AVP. AVP concentrations rose sharply in response to metoclopramide administration; the mean peak increase was observed 15 min after metoclopramide injection. In contrast, 10 mg domperidone did not modify plasma AVP levels at any time (Table 1). An identical pattern was observed when the higher dose (20 mg) of domperidone was used (data not shown). Neither metoclopramide, nor domperidone altered plasma osmolality or haematocrit (Table 2). Blood pressure remained constant in all subjects during all tests (Table 2); none of the subjects experienced side effects after metoclopramide or domperidone treatment.

Discussion

The data presented here confirm the stimulating effect of metoclopramide on AVP secretion. A similar finding has been reported by Nomura *et al.* (1984); however, at variance with our results, these authors described a biphasic increase of AVP at 15 and 90–120 min after metoclopramide injection and attributed the first increment to blockade of dopaminergic receptors in AVP secreting structures and the second peak to a concomitant fall in blood pressure. We did not observe this pattern in our subjects, since only an early AVP increase was found after metoclopramide, while blood pressure remained constant for at least 120 min after drug treatment. Similarly, blood osmolality and haematocrit did

Table 1 Effect of the i.v. injection of 10 mg of metoclopramide or 10 mg of domperidone on plasma AVP concentrations (pg ml^{-1}) in normal men. Each point represents the mean $\pm$ s.e. mean of 12 observations

	Time (min)							
	-15	0	15	30	45	60	90	120
Metoclopramide	2.6 ± 0.4	2.3 ± 0.3	4.0* ± 0.3	3.2** ± 0.2	2.3 ± 0.2	2.5 ± 0.2	2.4 ± 0.4	2.6 ± 0.4
Domperidone	2.7 ± 0.3	2.4 ± 0.3	2.6 ± 0.5	2.5 ± 0.2	2.4 ± 0.3	2.2 ± 0.4	2.3 ± 0.4	2.5 ± 0.4

* $P < 0.001$ vs values at time 0

** $P < 0.005$ vs values at time 0

Table 2 Effect of an injection of metoclopramide or domperidone on plasma osmolality, haematocrit and blood pressure. The values at each time interval represent the mean $\pm$ s.e. mean of 12 observations

		Time (min)							
		-15	0	15	30	45	60	90	120
Plasma osmolality (mosmol kg ⁻¹)									
Metoclopramide		286.4 ± 1.4	286.9 ± 1.3	286.6 ± 1.8	286.9 ± 1.4	287.0 ± 1.5	286.4 ± 1.3	285.7 ± 1.8	286.4 ± 1.6
Domperidone		285.1 ± 1.5	286.6 ± 1.4	288.0 ± 1.9	286.6 ± 1.6	287.5 ± 1.2	286.0 ± 1.4	286.2 ± 1.3	286.7 ± 1.5
Haematocrit (%)									
Metoclopramide		47.6 ± 1.4	47.8 ± 1.5	47.4 ± 1.9	47.1 ± 1.3	48.3 ± 1.4	48.7 ± 1.2	48.4 ± 1.4	48.5 ± 1.3
Domperidone		47.3 ± 1.8	46.8 ± 1.7	47.2 ± 2.0	46.8 ± 2.1	46.0 ± 1.9	46.5 ± 1.9	47.3 ± 2.0	47.2 ± 1.7
Blood pressure (mm Hg)									
Metoclopramide	systolic	120.7 ± 2.4	120.0 ± 2.6	120.3 ± 1.8	118.0 ± 2.4	120.0 ± 2.6	120.7 ± 2.3	119.7 ± 2.6	120.1 ± 2.8
	diastolic	76.8 ± 2.2	78.0 ± 1.9	74.0 ± 2.4	75.4 ± 1.9	76.8 ± 1.8	77.2 ± 1.9	76.0 ± 2.0	76.6 ± 1.9
Domperidone	systolic	122.6 ± 2.4	121.4 ± 2.0	120.5 ± 2.5	122.4 ± 2.5	121.3 ± 1.8	121.6 ± 1.5	123.3 ± 2.4	121.7 ± 2.2
	diastolic	77.4 ± 2.0	76.1 ± 1.7	75.8 ± 2.4	75.7 ± 2.7	75.0 ± 2.2	76.3 ± 2.0	74.8 ± 2.3	75.0 ± 2.6

not change during metoclopramide tests, suggesting that metoclopramide has a specific action on AVP release, which is independent of osmotic, barometric or volumetric variations.

Domperidone is a specific antidopaminergic agent which, in contrast with metoclopramide (Peringer *et al.*, 1976), does not cross the BBB (Baudry *et al.*, 1979; Laduron & Leysen, 1979) and is thus devoid of central dopamine blocking activity. In contrast with metoclopramide, domperidone did not modify circulating concentrations of plasma AVP, suggesting that metoclopramide stimulates AVP secretion by acting on structures located inside the BBB.

An alternative explanation is that metoclopramide and domperidone differ in their capacity for blocking dopamine receptors in the hypothalamic/pituitary regions. Another possibility is

that metoclopramide action is mediated non-specifically through modulation of other neurotransmitters. In this regard, evidence has accumulated on the role of metoclopramide as a stimulator of muscarinic-cholinergic (Chiodera & Coiro, 1984; Jungman *et al.*, 1984) and serotonergic (Fang & Shian, 1981; Chiodera *et al.*, 1984a; Jungmann *et al.*, 1984) receptors, which are known (particularly the former) to be involved in the mediation of AVP secretion (Sklar & Schrier, 1983).

Further studies are needed in order to gain a better insight of the mechanisms of action of metoclopramide on AVP secretion.

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