Differential actions of desipramine on sympathoadrenal release of noradrenaline and adrenaline

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Spillovers of noradrenaline (NA) and adrenaline (A) into plasma were examined before and after i.v. administration of 0.3–0.5 mg kg⁻¹ desipramine (DMI) in 19 normal volunteers. DMI decreased the total body spillover of NA by 20 ± 4%, but increased that of A by 45 ± 10%. The results indicate differential sympathoadrenal actions of DMI, characterized by inhibition of NA release from sympathetic nerves and stimulation of A secretion from the adrenals. These effects of DMI provide an explanation for some of the cardiovascular complications of tricyclic antidepressant therapy and may also help to explain how sympathoadrenal function is differentially regulated.

Keywords desipramine adrenaline noradrenaline neuronal uptake monoamine transporter adrenal medulla sympathetic nervous system

Introduction

The antidepressant effects of DMI are thought to result from blockade of neuronal reuptake of monoamines. This action would be expected to increase the availability of transmitter at neuroeffector sites. The effects of DMI on sympathetic nerves, however, are characterized by a decrease in NA turnover secondary to pronounced sympathoinhibition [1–4]. Reduction of sympathetic nerve activity after intracisternal injection of DMI in rabbits is accompanied by an increase in A release [5] indicating differential actions on sympathoneural and adrenomedullary outflows. The present study evaluated whether DMI elicits a similar dissociation of sympathoneural and adrenomedullary outflows in humans. Since changes in plasma catecholamines reflect changes in their plasma clearance as well as their release into the circulation [2], subjects received i.v. infusions of [³H]-labelled A and NA to examine the effects of DMI on rates of release (spillover) of catecholamines into the bloodstream.

Methods

Nineteen healthy male volunteers, aged 23 to 68 (mean 44) years, participated in the study. Procedures were approved by the appropriate human subjects

ethics review committees of the collaborating centres and each subject gave written informed consent. Subjects were studied in the morning, after abstaining from coffee and tea overnight.

A catheter percutaneously inserted into a radial or brachial artery under local anaesthesia was used to sample blood. A forearm venous catheter was used for concurrent infusion of [³H]-labelled NA and A ((-)-7- or (-)-[2,5,6-³H]-NA and (-)-[N-methyl-³H]A; New England Nuclear, Boston MA). Radiotracers were stored at -80° C in 0.05 M acetic acid containing 1 mM ascorbic acid; thawed aliquots were diluted in 0.9% sterile saline and infused at rates of 1 to 1.3 µCi min⁻¹ (0.2 or 0.4 ml min⁻¹).

Baseline arterial blood samples (10 ml) were collected with the subjects in the supine position, beginning at least 30 min after the start of radiotracer infusions. DMI hydrochloride (Ciba-Geigy; Australia or Sweden) was diluted in sterile 0.9% saline and infused i.v. through a second forearm venous catheter over 20 to 30 min (total dose of free base 0.3–0.5 mg kg⁻¹). This dose range has previously been shown to cause a 90% decrease in peroneal sympathetic nerve traffic and a 70% decrease in cardiac extraction of [³H]-NA in humans [3]. Further arterial blood samples were collected beginning 30 min after the end of the DMI infusion. At the conclusion of each study a sample of radiotracer infusate was retained

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for later analysis of [^3H]-labelled NA and A content.

Blood samples were collected into ice-chilled glass tubes (containing heparin or EGTA and glutathione), stored on ice and centrifuged (4°C) to separate the plasma at the end of studies. Samples of plasma and infusate were stored at -80°C until assayed for concentrations of endogenous and [^3H]-labelled A and NA by liquid chromatography with electrochemical detection coupled with fractionation of tritium eluents for counting by liquid scintillation spectroscopy [6].

Total body clearances (CL) and spillovers (S) of A and NA were estimated according to the equations below [2]

$$\text{CL} = I/[^3\text{H}]C \quad (1 \text{ min}^{-1}) \quad 1$$

$$S = \text{CL} \cdot C \quad (\text{nmol min}^{-1}) \quad 2$$

where I is the infusion rate (dpm min^{-1}), [^3H]C is the steady-state plasma concentration of [^3H]-labelled A or NA (dpm l^{-1}) and C is the plasma concentration of endogenous A or NA (nmol l^{-1}).

Data are expressed as means with variance for paired data before and after DMI shown using standard errors of the difference. Statistical significance was determined using analysis of variance or paired t -tests.

Results

Plasma concentrations of NA and A were changed in divergent ($F = 16.8$, $P < 0.001$) directions after i.v. DMI (Table 1). Administration of DMI decreased ($P < 0.02$) plasma NA concentrations by $7 \pm 4\%$, whereas plasma A concentrations were increased ($P < 0.01$) by $38 \pm 9\%$. DMI also caused divergent changes in total body clearances ($F = 9.8$, $P < 0.005$) and spillovers ($F = 25.6$, $P < 0.001$) of NA and A. The clearance of NA was decreased ($P < 0.002$) by $13 \pm 3\%$ after DMI, whereas that of A was unaffected. Thus, the total body spillover of NA into plasma was decreased ($P < 0.001$) by $20 \pm 4\%$ after DMI, whereas the rate of A release into plasma was increased ($P < 0.02$) by $45 \pm 10\%$ (Figure 1).

Table 1 Plasma concentrations, total body clearances and total body spillovers of A and NA before and after DMI

	Baseline	DMI	SED
Plasma NA (nmol l^{-1})	1.36	1.22	0.05†
Plasma A (nmol l^{-1})	0.31	0.40	0.03*
NA clearance (l min^{-1})	2.59	2.22	0.10†
A clearance (l min^{-1})	2.54	2.64	0.12
NA spillover (nmol min^{-1})	3.41	2.63	0.18†
A spillover (nmol min^{-1})	0.77	1.03	0.09*

Results are means with variance shown by standard errors of the difference (s.e.d.).

*Denotes an increase ($P < 0.02$), whereas † denotes a decrease ($P < 0.02$) after DMI.

Figure 1 Percentage changes in total body spillovers of NA and A after DMI. *Denotes a significant ($P < 0.02$) change in spillover. **Denotes a significant ($P < 0.001$) difference in NA and A spillover responses to DMI.

Discussion

The results show differential actions of DMI on sympathetic nerves and the adrenal medulla, characterized by decreased sympathoneural release of NA and increased release of A from the adrenals. This dissociated response pattern supports the growing body of evidence that sympathoneural and adrenomedullary outflows are differentially regulated.

Although the study did not include separate vehicle infusions, spillover of A tends to decrease, not increase, as subjects accustom to experimental procedures. The other observed changes are in agreement with previous findings and, thus, cannot be ascribed to infusion of saline. The DMI-induced decrease in total body clearance of NA, but not of A, is established to reflect less efficient neuronal uptake of A than NA [7]. The decrease in NA clearance attenuates the magnitude of the decrease in plasma NA concentrations resulting from the decrease in spillover. However, neuronal uptake blockade increases the fraction of NA released by nerves that escapes into plasma; thus, the decrease in NA spillover after DMI considerably underestimates the extent of sympatho-inhibition.

Evidence from studies in animals indicates that the sympatho-inhibitory effect of DMI results from activation of brainstem α_2 -adrenoceptors [8]; this occurs as a result of increased extracellular concentrations of catecholamines following blockade of their cellular uptake. Whether or not a similar mechanism is responsible for increased A release is not established. Decreases in sympathetic nerve traffic and increases in A release occur after other monoamine uptake blockers such as cocaine [9, 10] and (+)-oxaprotiline [11]; this supports the possibility that both the sympatho-inhibition and adrenal activation are related

to a primary site of action on monoamine transporters.

The divergent changes in sympathoneural and adrenomedullary outflows after neuronal uptake blockade do not represent isolated examples of heterogeneous responses of these systems. Ageing is associated with increased spillover of NA into plasma and decreased secretion of A [12]. Decreased sympathoneural outflow and increased A release occur during fasting [13], severe haemorrhagic hypotension [14] and syncope [15]. The effects of DMI are quali-

tatively similar to the latter effects and may therefore provide insight into the central nervous system mechanisms that govern stressor-specific differential regulation of sympathoneural and adrenomedullary outflows. Additionally, the divergent actions of DMI on sympathoneural and adrenomedullary outflows may explain some of the complications of tricyclic antidepressant therapy. Sympatho-inhibition may contribute to the side effects of orthostatic hypotension and dizziness, while increased A release might contribute to electrocardiographic abnormalities.

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