

## Review

# Clinical review: Immunomodulatory effects of dopamine in general inflammation

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Published online: 3 June 2004

*Critical Care* 2004, **8**:485-491 (DOI 10.1186/cc2879)

This article is online at <http://ccforum.com/content/8/6/485>

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## Abstract

Large quantities of inflammatory mediators are released during the course of endotoxaemia. These mediators in turn can stimulate the sympathetic nervous system (SNS) to release catecholamines, which ultimately regulate inflammation-associated impairment in tissue perfusion, myocardial impairment and vasodilatation. Treatment of sepsis is based on surgical and/or antibiotic therapy, appropriate fluid management and application of vasoactive catecholamines. With respect to the latter, discussions on the vasopressor of choice are ongoing. Over the past decade dopamine has been considered the 'first line' vasopressor and is frequently used to improve organ perfusion and blood pressure. However, a growing body of evidence indicates that dopamine has deleterious side effects; therefore, its clinical relevance seems to be more and more questionable. Nevertheless, it has not been convincingly demonstrated that other catecholamines are superior to dopamine in this respect. Apart from its haemodynamic action, dopamine can modulate immune responses by influencing the cytokine network. This leads to inhibition of expression of adhesion molecules, inhibition of cytokine and chemokine production, inhibition of neutrophil chemotaxis and disturbed T-cell proliferation. In the present review we summarize our knowledge of the immunomodulatory effects of dopamine, with an emphasis on the mechanisms by which these effects are mediated.

**Keywords** adhesion molecules, cytokines, dopamine, hemostasis, sepsis

## Introduction

The challenge to the immune system that occurs in endotoxaemia involves stimulation of immune cells to produce large amounts of inflammatory cytokines (e.g. IL-1, IL-6 and tumour necrosis factor [TNF]- $\alpha$ ). These mediators stimulate both the hypothalamic-pituitary-adrenal axis and the systemic-adrenomedullary sympathetic nervous system (SNS). Consequently, catecholamines are released from preganglionic efferent and postganglionic SNS fibres, innervating a wide range of target organs and thereby

regulating endotoxin-induced alterations in vascular resistance and tone, tissue perfusion, cardiac and renal function, and hormone release. Although dopamine is also released, noradrenaline (norepinephrine) and adrenaline (epinephrine) appear to be the principal neurotransmitters in this respect. In early and late stages of severe inflammation, catecholamine production is significantly increased [1]. Nevertheless, it must be noted that circulating catecholamines are poor markers of SNS activation during acute stress, such as occurs in sepsis [2].

CREB = cAMP responsive element binding protein; IL = interleukin; LPS = lipopolysaccharide; MAO = monoamine oxidase; NF- $\kappa$ B = nuclear factor- $\kappa$ B; NO = nitric oxide; PBMC = peripheral blood mononuclear cell; PKA = protein kinase A; ROS = reactive oxygen species; SNS = sympathetic nervous system; TNF = tumour necrosis factor.

Apart from their haemodynamic effects, circulating catecholamines themselves can modulate the cytokine network and thereby regulate both suppressive and stimulatory effects on immune responses. Whereas stimulation of  $\alpha$ -adrenoceptors is associated with induction of TNF- $\alpha$  or IL-1 in monocytes,  $\beta$ -adrenergic receptor stimulation is commonly regarded to mediate anti-inflammatory effects (i.e. inhibition of TNF- $\alpha$ , IL-1, IL-6 and concomitant induction of IL-10 production) [3].

Dopamine synthesis is induced rapidly under inflammatory conditions. Serum dopamine concentrations are further increased by therapeutic intervention with dopamine. The effects of low-dose treatment (i.e. up to 3  $\mu$ g/kg per min) are mediated primarily via dopaminergic receptors. Their activation results in inhibition of platelet aggregation [4], induction of vasodilatation in renal, mesenteric, cerebral and coronary vessels, as well as increased systemic blood pressure and flow [5]. Therefore, over the past two decades dopamine has been considered to be and recommended as the 'first line' vasopressor [6]. Several clinical studies have now evaluated the renoprotective effect of low-dose dopamine treatment. These data indicate that dopamine may increase urine output in critically ill patients, but that it neither prevents nor improves acute renal failure [7]. Similarly, whether dopamine has beneficial effects on splanchnic blood flow is also a subject of controversy [8]. In higher concentrations (3–5  $\mu$ g/kg per min), dopamine has positive inotropic effects and causes vasodilatation in the microcirculation via  $\beta_1$  and  $\beta_2$  adrenergic receptors, respectively [9]. Dopamine concentrations above 5  $\mu$ g/kg per min induce platelet aggregation and  $\alpha_1$  receptor mediated vasoconstriction, resulting in decreased microvascular blood flow [10].

It must be stressed, however, that the effect of dopamine might vary from one patient to another and depends on the state of disease [11]. Thus, in septic patients  $\beta$ -adrenergic effects might predominate, even at high dopamine concentrations [12]. This is attributed to different haemodynamic and cardiovascular functions, and to different tissue and body fluid distributions in these patients. Furthermore, in patients with hepatic or renal insufficiency, dopamine serum concentrations may reach even higher levels because of decreased clearance [13].

In contrast to the well recognized immunomodulatory effects of noradrenaline and adrenaline, the influence of dopamine on inflammatory responses are incompletely defined and controversially discussed. Most of our understanding of the nonhaemodynamic effects of dopamine comes from studies performed in the field of Parkinson's disease [14]. Recent studies have also indicated that treatment of kidney donors with dopamine improves long-term graft survival after kidney transplantation [15], possibly due to induction of antioxidants such as heme oxygenase 1 [16] or by reducing hypothermic preservation related transplant injury [17].

To enable a better understanding of the role of dopamine in modulating inflammatory responses, the present review summarizes the possible mechanisms of dopamine's action (Table 1).

## Dopamine: mechanisms of action

### Receptor mediated mechanisms

Dopamine induced immunomodulation is dose dependently mediated by different types of receptors (Table 2): the dopaminergic  $D_1$  ( $D_1/D_5$ ) and  $D_2$  ( $D_2/D_3/D_4$ ) receptors, as well as the  $\alpha$  and  $\beta$  adrenergic receptors.

#### *Dopaminergic receptors*

Whereas  $D_1$  receptors are known to be present on smooth muscle cells, endothelial cells, platelets, lymphocytes and natural killer cells [18,19], their presence on monocytes/macrophages is still questioned. Stimulation of  $D_1$  receptors, as demonstrated by the use of the selective  $D_1$  antagonist SCH 23390 [20], results in activation of adenylate cyclase and subsequently generation of cAMP, which in turn activates protein kinase A (PKA) [21]. Activation of cAMP responsive element binding protein (CREB) and PKA can inhibit translocation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) by retarding the degradation of the inhibitor of NF- $\kappa$ B, namely I $\kappa$ B- $\alpha$  [22]. Because NF- $\kappa$ B appears to be among the transcription factors that have been implicated in the expression of a wide range of proinflammatory genes, dopamine induced immune modulation can be explained via this pathway. NF- $\kappa$ B and CREB compete for the same KIX binding site on the coactivator molecule CREB-binding protein and are transcriptionally active if they are bound to CREB-binding protein only [23]. Therefore, dopamine induced CREB activation also results in diminished NF- $\kappa$ B dependent transcription, and hence in an impairment of the inflammatory response. Similar to  $D_1$  receptors, stimulation of  $D_2$  receptors, which are expressed on lymphocytes [24], endothelial cells [20] and platelets [19], leads to generation of cAMP and inhibits the NF- $\kappa$ B dependent transcription cascade. However, there are also reports indicating that stimulation of  $D_2$  receptors activates NF- $\kappa$ B in a time and dose dependent manner [25].

#### *$\alpha$ and $\beta$ Adrenergic receptors*

Most inflammatory cells express  $\alpha$  and  $\beta$  adrenoreceptors. Although  $\alpha_1$  adrenoreceptor stimulation does not seem to play a role in inflammatory responses, activation of  $\alpha_2$  receptors has a marked influence on inflammatory cells. Stimulation of  $\alpha_2$  receptors induced the production of a variety of proinflammatory cytokines (e.g. TNF- $\alpha$ , IL-1 and IL-6) and anti-inflammatory cytokines (e.g. IL-10).  $\alpha_2$  Receptor mediated cytokine production is regulated via activation of protein kinase C, phosphorylation of I $\kappa$ B and subsequently activation of NF- $\kappa$ B [26].

The  $\beta$ -adrenergic receptors, predominantly  $\beta_2$ , are also coupled to the cAMP-PKA pathway. Hence, stimulation of

**Table 1****Immunomodulatory effects of dopamine under septic conditions**

Influence on		Effect	Mechanism
Pituitary hormones	Prolactin	Suppression	Indirectly via nNOS, D <sub>2</sub> receptor
	Thyroid hormones	Suppression	D <sub>2</sub> receptor
	Growth hormones	Suppression	D <sub>2</sub> receptor
	Glucocorticoid	Induction	α <sub>2</sub> receptor, D <sub>2</sub> receptor
Cytokines	IL-10	Induction	β receptor, ROS
	TNF-α (monocytes, HUVECs)	Suppression	β receptor, ROS
	TNF-α (neutrophils)	Suppression	D <sub>1</sub> receptor
	IL-1	Suppression	β receptor, ROS
	IL-6 (monocytes, HUVECs)	Suppression	β receptor, ROS
	IL-6 (glomerulosa cells)	Induction	D <sub>2</sub> receptor
	IL-12 p40	Suppression	β receptor
Chemokines	IL-8 (HUVEC)	Induction	ROS
	IL-8 (PTEC)	Suppression	ROS
	Gro-α	Suppression	ROS
	ENA-78	Suppression	ROS
Adhesion molecules	CD11b/CD18	Suppression	ROS
	E-selectin	Suppression	ROS?
	ICAM-1	Suppression	ROS?
Nitric oxide	In HUVECs	Suppression	ROS
	In monocytes	Induction	β receptor
Apoptosis	In neutrophils	Induction	D <sub>1</sub> and β receptor, ROS
	In lymphocytes	Induction	D <sub>1</sub> and β receptor, ROS
PLA <sub>2</sub> metabolites	PAF	Suppression	?
Respiratory burst	In neutrophils	Suppression	D <sub>1</sub> receptor

HUVEC, human umbilical vein endothelial cell; ICAM, intercellular adhesion molecule; IL, interleukin; nNOS, neuronal nitric oxide synthase; PAF, platelet activating factor; PTEC, proximal tubular epithelial cell; ROS, reactive oxygen species; TNF, tumour necrosis factor.

**Table 2****Dopaminergic receptor stimulation**

Dopamine concentration	Receptor					
	α <sub>1</sub> adrenergic	α <sub>2</sub> adrenergic	β <sub>1</sub> adrenergic	β <sub>2</sub> adrenergic	Dopamine D <sub>1</sub>	Dopamine D <sub>2</sub>
0–3 µg/kg per min	0	0	+	0	+++	+++
3–5 µg/kg per min	+	+	+++	++	++++	++++
>5 µg/kg per min	+++	+	+++	+	++++	++++

these receptors inhibits the transcription of NF-κB regulated proinflammatory genes in a manner similar to that described above [27]. Furthermore, cAMP can also indirectly activate CCAAT/enhancer binding protein [28], which, together with CREB/activating transcription factor, is believed to be largely

responsible for β<sub>2</sub> adrenoceptor mediated IL-10 production in monocytes [29].

IL-10 inhibits lipopolysaccharide (LPS) mediated TNF-α production both *in vivo* and *in vitro* [30], and it can therefore

be considered part of a host protective mechanism during endotoxaemia. However, van der Poll and coworkers [31] found that in LPS-stimulated blood the increase in IL-10 levels caused by adrenaline only marginally contributed to concurrent inhibition of TNF- $\alpha$  production. These conclusions emphasize that the role of IL-10 as a causal factor in immunosuppression remains controversial.

### Oxidative stress

Dopamine also mediates cellular effects, independent of or in conjunction with receptor activation. The clearance of dopamine depends in part on its rate of degradation by monoamine oxidase (MAO)-A and MAO-B [32], which catalyzes the oxidative deamination of dopamine. Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) is generated as a consequence of MAO mediated degradation of dopamine [33]. In the presence of Fe<sup>2+</sup> this is further converted through the Fenton reaction into highly reactive hydroxyl radicals (HO<sup>•</sup>). H<sub>2</sub>O<sub>2</sub> and HO<sup>•</sup> have been found to have both beneficial and deleterious effects on cells, depending on the concentration and cellular system in which they were studied. Reactive oxygen species (ROS) act as intracellular messengers activating multiple signalling pathways, including activation of c-Jun N-terminal kinase, extracellular signal regulated kinases, NF- $\kappa$ B and activator protein-1 [34].

Low concentrations of ROS improve the cellular redox status by increasing the amount of endogenous antioxidants such as superoxide dismutase, heme oxygenase 1 and ferritin [35]. However, as a consequence of their aggressive nature, high concentrations of ROS inevitably result in cytotoxicity and genotoxicity.

Dopamine can also form reactive metabolites through auto-oxidation. Because of the unstable nature of the catechol group, it can be oxidized to reactive quinone molecules, which themselves exert toxic effects. Although oxidation of dopamine is primarily mediated via ROS [36], a number of enzymes are able to catalyze dopamine quinone formation, including prostaglandin H synthase, xanthin oxidase and tyrosinase [37]. This auto-oxidation is prevented by antioxidants (e.g. ascorbic acid) [38]. It has been suggested that the toxicity of dopamine quinones is mediated via protein and DNA damage, ultimately leading to apoptosis [39].

### Effects of dopamine on the neuroendocrine system

The production of proinflammatory cytokines and chemokines by monocytes/macrophages and endothelial cells under septic conditions is well documented. Severe inflammation is accompanied by alterations in activity of the neuroendocrine system. In the early stage of inflammation hormone release is stimulated, whereas in the late phase its release is suppressed [40]. Therefore, marked variations in serum cortisol, thyroid hormone, growth hormone and prolactin concentrations occur during the course of systemic inflammation. Dopamine suppresses the release of most if not

all anterior pituitary dependent hormones [41], but at the same time it stimulates the synthesis of adrenal glucocorticoids via  $\alpha_2$  and D<sub>2</sub> receptors [42]. The changes induced in the hypothalamic–pituitary–adrenal axis by dopamine when it is administered in the early phase of severe inflammation are similar to those that occur in the late phase without dopamine treatment [41].

Bacterial LPS affects pituitary hormone secretion, including prolactin release, by inducing synthesis and release of cytokines such as TNF- $\alpha$  [43]. It is now generally accepted that prolactin can enhance monocyte, and T-cell and B-cell immune responses under normal conditions, and has beneficial effects on cell-mediated immunity after haemorrhage [44]. Because prolactin is mainly under the inhibitory control of dopamine, decreased serum prolactin concentration might lead to compromised immune function and hence susceptibility to infection [45]. Several studies have shown that therapeutic intervention with dopamine in critically ill infants and adults dramatically decreases serum prolactin concentrations, thereby questioning the use of dopamine in these patients [46].

### Effects of dopamine on the production of inflammatory mediators

#### Endothelial cells

The barrier function of endothelial cells is important in preventing vascular leakage and free migration of inflammatory cells. During sepsis impairment in barrier functions allows plasma proteins to enter into the interstitium, supporting oedema formation. The barrier function is further impaired by mononuclear cells, which first adhere to the endothelium and then are triggered to leave the circulation via migration between endothelial cells. D<sub>1</sub> and D<sub>2</sub> dopamine receptors are present on endothelial cells, rendering them responsive to dopamine. Both *in vitro* and *in vivo* studies have shown that dopamine inhibits LPS mediated up-regulation of adhesion molecules expressed on macrovascular and microvascular endothelial cells [47], with a concomitant decrease in neutrophil migration [48]. Interestingly, dopamine has a dual effect on endothelial chemokine production. Although basal and LPS mediated production of growth-related-gene  $\alpha$  (Gro- $\alpha$ ) and epithelial neutrophil activating protein-78 (ENA-78) are significantly downregulated by dopamine, the reverse has been found for IL-8 [47]. This effect is still observed when the cells are stimulated with LPS for up to 3 hours before dopamine administration. Neither dopaminergic nor adrenergic receptor antagonist were able to influence this action of dopamine. In contrast, addition of antioxidants completely prevented the action of dopamine, suggesting a pivotal role for oxidative stress. Although addition of H<sub>2</sub>O<sub>2</sub> to microvascular endothelial cells yielded results similar to those with dopamine stimulation, neither the MAO inhibitor pargylin nor the dopamine uptake inhibitor GBR 12909 was able to inhibit the effects of dopamine.

## Neutrophils

During inflammatory responses neutrophils are among the first cell types that leave the microcirculation and enter into the inflammatory site. Dopamine uptake, storage and synthesis by these cells have been described [49]. Dopamine treatment may lead either directly or indirectly to a functional suppression of neutrophils, which was demonstrated for transmigration of stimulated neutrophils after dopamine administration. This was mediated by a decreased neutrophil adhesion to endothelial cells caused by a reduction in CD11b/CD18 expression on neutrophils, and by attenuation of the chemoattractant effect of IL-8 required for trans-endothelial migration of neutrophils [48]. In addition, pharmacological concentrations of dopamine induce apoptosis in neutrophils isolated from healthy volunteers and reverse delayed apoptosis of neutrophils in septic patients [50]. These effects are not receptor mediated because the D<sub>1</sub> agonist fenoldopam did not influence neutrophil behaviour. In contrast, the effects of dopamine on respiratory burst, phagocytosis [51,52] and TNF- $\alpha$  release are probably D<sub>1</sub> receptor dependent [52].

## Monocytes/macrophages

It was shown that macrophages can release or store dopamine in cytoplasmic vesicles [53], but the presence of dopaminergic receptors on monocytes/macrophages has not clearly been demonstrated [54]. During the early phase of inflammation, cytokines such as TNF- $\alpha$ , IL-1, IL-12 p40 and IL-6, and chemokines such as IL-8 are highly upregulated in monocytes/macrophages. Dopamine or dopamine agonists significantly inhibited this [55]. In accordance with those findings, treatment with the dopamine antagonist metoclopramide stimulated constitutive and inducible expression of proinflammatory cytokines *in vitro* [43], whereas it suppressed chlorpromazine induced production of the anti-inflammatory cytokine IL-10 *in vivo* [56]. The effects of dopamine on cytokine production are mainly mediated via  $\beta$  adrenoceptors because the action of dopamine was partly prevented by propranolol and not influenced by dopaminergic receptor antagonists [57]. Because propranolol reversed the effect of dopamine, it has been suggested that receptor independent mechanisms might also play a role. Dopamine induced ROS are most likely involved in mediating changes in monocyte/macrophage phenotype and function [58].

Basal nitric oxide (NO) production by macrophages is not altered, or only minimally, by dopamine, whereas LPS induced NO production is strongly increased via  $\beta$  receptor stimulation [59]. This mechanism might contribute to the increased NO production found in critically ill patients.

## Lymphocytes

Among the catecholamines, adrenaline and noradrenaline are the ones that have been most extensively investigated for their regulatory effects on immune responses in lymphocytes, antigen presenting cells and natural killer cells [60]. The

synthesis and release of dopamine by lymphocytes, as well as the presence of D<sub>1</sub> receptors, suggest regulation of functional activities such as lymphocyte proliferation, differentiation and cytokine production [61]. *In vitro* experiments with dopamine or the dopamine receptor agonist bromocriptine revealed a significant inhibition of lymphocyte proliferation, which was mediated either by dopaminergic receptors [62] or by ROS [63]. Furthermore, selective effects on T-cell mediated immunity (i.e. downregulation of delayed-type hypersensitivity responses) have also been described [64]. Similarly, in blood of septic patients receiving dopamine, a decrease in *in vitro* T-cell proliferation in response to concanavalin has been observed [46]. In contrast, *in vivo* experiments in mice using dopamine or D<sub>1</sub> and D<sub>2</sub> receptor agonists showed stimulation of basal B-cell and T-cell proliferation, and augmented LPS-induced proliferation [65]. These effects may also be indirectly mediated by influencing the microenvironment and mediator production by accessory cells [24].

## Effects of dopamine on apoptosis

Dopamine is involved in the modulation of apoptosis in both neuronal and non-neuronal cells. There is evidence that dopaminergic mechanisms may contribute to neurodegeneration in Parkinson's disease. In striatal neurones high concentrations of dopamine are proapoptotic; however, low concentrations of dopamine prevent cell death, possibly due to the ability of dopamine to affect intracellular oxidative processes [66]. It is currently believed that excessive oxidant stress, induced by metabolism of dopamine, plays a major role in the pathogenesis of the selective nigrostriatal neuronal loss that occurs in Parkinson's disease. It was recently shown that dopamine, in physiological concentrations, is capable of initiating apoptosis in cultured, postmitotic sympathetic neurones. Stable transfection of Bcl-2 in PC-12 pheochromocytoma cells was able to inhibit dopamine mediated apoptosis [67]. Dopaminergic modulation of apoptosis has also been investigated in human peripheral blood mononuclear cells (PBMCs) obtained from healthy donors. Dopamine treatment at low concentrations reduced spontaneous apoptosis, whereas apoptosis was enhanced at higher concentrations. At low dopamine concentrations this was inhibited by the D<sub>1</sub>-like receptor antagonist SCH 23390, but not by the D<sub>2</sub>-like receptor antagonists domperidone or haloperidol. At high concentrations the effect was prevented by the antioxidants glutathione or *N*-acetyl-L-cysteine [68]. Dopamine does not affect the expression of Cu/Zn superoxide dismutase or Bcl-2 in PBMCs. In human PBMCs, dopamine appears to promote apoptosis through oxidative mechanisms but it may also rescue cells from apoptotic death, possibly through activation of D<sub>1</sub>-like receptors. Other authors have suggested that dopamine induced apoptosis in lymphocytes is mediated by  $\beta$  receptors [69]. The dual effect of dopamine on human PBMCs closely resembles that on striatal neurones.

## Conclusion

Because dopamine can have adverse effects on organ function during septic processes, clinical use of dopamine is increasingly being questioned. However, clinically relevant concentrations of dopamine also inhibit inflammation induced upregulation of cytokines, chemokines and adhesion molecules, and induce the production of anti-inflammatory mediators. Because of its immunomodulatory effects, dopamine might gain a new therapeutic role in the treatment of immunological dysregulation. To evaluate the immunomodulatory potential of dopamine, more clinical studies conducted in patients with or without severe inflammation would be useful.

## Competing interests

The author(s) declare that they have no competing interests.

## Acknowledgement

Thanks to the Forschungsfond of University of Mannheim for supporting the work of the authors cited in the present review.

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