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Pharmacological strategy designed to limit ischemia-reperfusion injury in brain dead donor kidneys

Stratégies pharmacologiques pour limiter les lésions d'ischémie-reperfusion des greffons de donneurs en état de mort encéphalique

J. Branchereau^{a,*}, B. Barrou^b

^aService d'Urologie, CHU de Nantes - Hôtel-Dieu, 1 place Alexis Ricordeau, 44093 Nantes Cedex 1, France

^bINSERM, U1087, Ischémie-reperfusion en transplantation d'organe : mécanismes et innovations thérapeutiques, Poitiers ; université de Poitiers, faculté de Médecine et de Pharmacie, 86021 Poitiers, France

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Summary

Ischemia-reperfusion injury is a complex physiological process responsible for delayed renal function or primary graft non-function, explicitly when kidney allograft are issued from expanded criteria donor. The purpose of this review is to detail the detrimental phenomena altering kidney allograft's integrity in brain dead donor, therefore suggesting pharmacological interventions aiming to reduce ischemia-reperfusion injuries and improving transplantation outcome. This ischemia-reperfusion phenomenon must therefore be anticipated through the whole procedure starting at the stage of conditioning of the potential donor. Hormonal and haemodynamic consequences of brain death modify perfusion and oxygenation conditions of the organs. Thus, after describing the autonomic, metabolic, endocrine and chemokine storm occurring during brain death, the authors focus on strategies to prevent hemodynamic instability in the donor and to limit the consequences of hormonal and immunological changes on organs that will eventually be transplanted.

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*Corresponding author.

E-mail address: julienbranchereau@gmail.com (J. Branchereau).

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Résumé

L'ischémie-reperfusion est un processus aux voies de signalisations complexes et aux conséquences cliniques parfois délétères en transplantation rénale (reprise retardée de fonction ou non fonction primaire), surtout lorsque le transplant est issu d'un donneur à critères élargis. Le but de cette revue est de décrire les phénomènes physiopathologiques survenant chez les donneurs en état de mort encéphalique pour suggérer des stratégies d'intervention pharmacologiques. Ainsi, la compréhension des mécanismes de l'orage dysautonomique, cytokinique et hormonal survenant pendant la mort encéphalique, peut permettre de proposer une prise en charge optimale du risque d'instabilité hémodynamique du donneur et de prévenir les conséquences immunologiques sur l'organe transplanté. L'objectif étant alors de proposer des options thérapeutiques chez le donneur en mort encéphalique visant à limiter les lésions d'ischémie reperfusion du transplant et à améliorer les résultats de la transplantation.

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Introduction

The growing shortage of donor kidneys has led to the search for new sources and the use of kidneys from Expanded Criteria Donor (ECD). ECD donors are normally aged 60 years or older, or over 50 years with at least two of the following conditions: hypertension history, serum creatinine > 1.5 mg/dl or cause of death from cerebrovascular accident. Ischemia-reperfusion injury is a complex physiological process responsible for delayed recovery of renal function or primary graft non-function. Expanded criteria donor kidneys are particularly susceptible to ischemia-reperfusion injury. This ischemia-reperfusion phenomenon must therefore be anticipated throughout the procedure, i.e. right from the stage of conditioning of the potential donor until post-conditioning of the kidney. The purpose of this review of the literature is to identify the various pharmacological strategies that can be used in brain dead donors in order to limit ischemia-reperfusion injury during renal transplantation.

Autonomic, metabolic and endocrine storm induced by brain death

Brain death initially induces vagal hyperactivity causing bradycardia, hypotension and decreased cardiac output. Necrosis of the parasympathetic nuclei of the medulla oblongata then triggers an autonomic storm mediated by an increased release of catecholamines (adrenaline, noradrenaline, dopamine) which in turn. Results in tachycardia, high blood pressure and peripheral vasoconstriction and also has cardiac repercussions such as the formation of zones of myocardial necrosis and conduction disorders. Although myocardial contractility is increased, left ventricular ejection fraction is decreased due to the massive increase of systemic vascular resistance. Finally, destruction of spinal cord sympathetic pathways leads to loss of autonomic regulation, resulting in peripheral vasodilatation, arterial hypotension and organ hypoperfusion.

Major hormonal changes are also observed following necrosis of the hypothalamo-pituitary axis. Diabetes insipidus occurs as a result of decreased ADH (antidiuretic hormone)

and ACTH (adrenocorticotrophic hormone) secretion. Non-treated diabetes insipidus contributes to deterioration of hypovolaemia and cardiovascular instability. The thyroid hormone, triiodothyronine (T3), becomes undetectable during the hours following brain death, while thyroxine (T4) remains at detectable levels. Thyroid stimulating hormone (TSH) does not increase in response to this fall in T3. The corticotrophic axis is also affected with a marked reduction of ACTH secretion, resulting in adrenal insufficiency, although this effect remains controversial, as some authors have shown that cortisol levels remain unchanged [1], or may be decreased [2] or even increased [3].

Haemoglobin increases transiently due to the appearance of a third compartment. Haematocrit then decreases as a result of dilution induced by fluid resuscitation solutions, as well as haemolysis.

Brain death is followed by endothelial activation with increased production of cytokines (IL-1, IL-6, IL-8), inducing platelet aggregates. This endothelial activation induces a hypercoagulability state associated with disseminated intravascular coagulation. The levels of a very large number of cytokines (IL-1, IL-1, IL-6, IL-8, IL-10, IL-12, TNF α) and proteins known to play a role in inflammatory cell adhesion and activation (E-selectin, ICAM-1, VCAM-1, neopterin, β 2-microglobulin, IL-2 receptor-fragment) increase following head injury

Brain death is therefore responsible for major haemodynamic, endocrine and metabolic disorders predisposing to the development of ischemia-reperfusion injury. The challenge of renal transplantation is to preserve the viability and function of donor kidneys.

Prevention of haemodynamic instability**Fluid resuscitation**

Fluid resuscitation plays a critical role in donor conditioning. Management of brain dead donors requires large quantities of crystalloids to prevent hypotension, resulting sometimes in severe tissue oedema.

Hydroxyethylstarch (HES) is hydrolysed *in vivo* by serum amylase, and is then excreted by the kidneys. Plasma accumulation of high molecular weight HES (200 kD) has deleterious effects with accentuation of ischemia-reperfusion injury IRI and consequently DGF delayed recovery of renal function [4], but with no effect on long-term renal function [5]. However, this adverse event has only been observed with high molecular weight HES, while medium molecular weight solutions (130 kD) have a less marked impact on renal function [6].

Dopamine

Dopamine has dose-dependent cardiovascular effects. At low doses, it predominantly stimulates vascular D1 receptors, leading to selective renal, mesenteric, cerebral and coronary vasodilatation. At higher doses, dopamine predominantly acts on cardiac β_1 receptors, inducing positive inotropic effects. At very high doses, the action of dopamine on vasoconstrictor receptors results in the elevation of blood pressure. Schnuelle showed that the use of dopamine and noradrenaline in brain dead donors was associated with a lower rate of ischemia-reperfusion injury lesions and consequently better long-term graft survival [7]. The same author [8] confirmed these data in a randomized prospective series of 264 haemodynamically stable brain dead donors. Low-dose dopamine infusion (4 $\mu\text{g}/\text{kg}/\text{min}$) was an independent predictive factor of early recovery of graft function and consequently decreased the number of post-transplantation dialysis sessions. The effect was not explained by a better control of haemodynamic parameters, (as donors studied were haemodynamically stable), but rather by the protection of endothelial cells from the effects of the IRI-induced oxidative stress. In fact, apart from stimulating specific receptors, dopamine also acts directly on the cell membrane at clinically relevant concentrations and is able to protect endothelial cells from oxidative stress during cold storage. The mechanism of action of dopamine is related to the cyclic dihydroxyphenolic structure of the dopamine molecule, which delays the hypothermic cell destruction process due to intracellular adenosine triphosphate depletion and intracellular calcium accumulation.

Vasopressin

Vasopressin is an antidiuretic hormone synthesised by the *supra*-optic and paraventricular nuclei of the hypothalamic axis. It mainly has an antidiuretic role, but also exerts a major vasoconstrictor action [9]. It binds to AVPR1 receptors of vascular smooth muscle fibres, thereby inducing vasoconstriction. Pennefather and al. [10] showed that vasopressin administration to the donor decreased dopamine requirements and increased blood pressure while maintaining cardiac output. Previous studies showed that donor vasopressin administration resulted in the accentuation of graft tubular necrosis lesions, related to the vasoconstrictor effect of vasopressin [9]. However, several randomized studies [11-12] have demonstrated the marked superiority of vasopressin compared to adrenaline on donor cardiac function and graft function.

Desmopressin

Desmopressin (1-desamino-8-D-arginine vasopressin) is a vasopressin analogue with a less intense vasoconstrictor action, but a more intense antidiuretic action. In a randomized prospective series of 97 donors, Guesde¹³ showed that desmopressin allowed good control of diabetes insipidus with reduction of donor diuresis while preserving short- and long-term renal graft function. In a recent multicentre, retrospective trial, Benck [14] showed that administration of desmopressin (1-desamino-8-D-arginine vasopressin, DDAVP) to the donor significantly improved overall survival of renal grafts (85.4% vs. 73.6%, $P = 0.003$). Desmopressin also had a beneficial action on coagulopathy induced by brain death.

Prevention of endothelial activation and oxidative stress

Hydrocortisone

Administration of hydrocortisone to the donor decreases the catecholamines requirements such as noradrenaline by 30 to 58% [15]. Corticosteroids also have an anti-inflammatory action by preventing the release of cytokines (such as tumour necrosis factor alpha, interleukin 1, interleukin 6) and adhesion molecules (such intercellular adhesion molecule type 1, E-selectin).

Selectin-P antagonists and C1 and C5 inhibitors

YSPSL selectin-P antagonists (rPSGL-Ig - recombinant P-selectin glycoprotein ligand) [16] and the selectin ligand inhibitor, TBC 1269, decrease binding of immune cells onto the endothelial wall of renal grafts. Complement activation has been shown to be an early event in I/R injury. Therefore, inhibition of complement activation or its components could be a protection after reperfusion. C1 and C5 inhibitors [17] have also been shown to be useful to limit ischemia-reperfusion injury.

Melatonin

Excessive production of free radicals plays a major role in constitution of ischemia-reperfusion injury, as these free radicals contribute to necrosis and cell apoptosis phenomena. Melatonin (N-acetyl-5-methoxytryptamine) is a powerful antioxidant agent, widely used in the prevention of IRI not only directly neutralizing free radicals [18], but also by stimulating several antioxidant and cell membrane-stabilizing enzyme systems [19]. Melatonin and its metabolites are associated with very little toxicity and very good safety [20]. Several studies have demonstrated the value of the antioxidant effects of melatonin in prevention of ischemia-reperfusion injury, especially in experimental models of warm ischemia. However, few studies have assessed the value of melatonin

on cold ischemia models. In 2009, in an experimental study on a model of renal transplantation, Li [21] reported that donor preconditioning with melatonin protected the graft from ischemia-reperfusion injury.

Trimetazidine

Trimetazidine dihydrochloride is a selective inhibitor of the final enzyme (3-ketoacyl coenzyme A thiolase) of the fatty acid beta-oxidation pathway in the mitochondrial matrix, thereby preventing intramitochondrial oedema. Long-chain fatty acids can be harmful to the cell because they require more oxygen than glucose to produce an equivalent quantity of ATP. Trimetazidine reduces the accumulation of metabolic wastes, particularly the accumulation of hydrogen ions, and therefore corrects electrolyte abnormalities by optimizing mitochondrial oxygen consumption and thereby restoring intracellular ATP synthesis. Trimetazidine protects the mitochondrion by releasing calcium accumulated in the mitochondrial matrix and by restoring membrane impermeability [22]. Trimetazidine is useful to limit ischemia-reperfusion injury. Addition of trimetazidine to organ preservation solutions reduces oxidative stress and acidosis and promotes energy metabolism [23].

Statins

Administration of statins to the donor for their anti-inflammatory effects is currently under evaluation in preclinical models of renal transplantation in the rat [24].

Prevention of the hormonal consequences of brain death

Antidiuretic hormone deficiency induced by necrosis of the hypothalamo-pituitary axis is responsible for diabetes insipidus. Diabetes insipidus induces massive polyuria and major fluid and electrolyte disorders (hypernatraemia, hypokalaemia, hypomagnesaemia, hypocalcaemia, hypophosphataemia). The objective of treatment is to restore blood volume and serum sodium. Blood volume compensation may be sufficient, but simple compensation may induce pulmonary oedema and consequently increase haemodynamic instability.

Thyroid hormones

Several retrospective studies have demonstrated the value of donor thyroid replacement therapy, especially in terms of haemodynamic stability and heart transplant function [25]. However, this action on haemodynamic stability was not confirmed by many other studies [26]. Furthermore, in a randomized prospective study, Goarin [27] showed that T3 therapy did not provide any benefit in terms of left ventricular ejection fraction. According to Lopez Haldon, donor hypothyroidism was not correlated with accentuation of myocardial damage. Donor T3 levels did not influence

kidney graft function [26]. The majority of non-randomized series concluded on the benefit of donor thyroid replacement therapy, but these results were not confirmed by randomized series [28]. Similarly, a meta-analysis of randomized trials did not show any significant difference in haemodynamic stability or kidney graft function between donors treated with thyroid hormones and those treated with placebo [28]. However, in a randomized prospective series, Garcia-Fages [29] demonstrated the value of thyroid replacement therapy on donor kidney adenine nucleotide levels.

Cortisol

Brain death induces decreased ACTH production and consequently adrenal insufficiency, although this effect is the subject of debate, as some authors have shown that cortisol levels remain unchanged [1], or may be decreased [30] or even increased [3]. Donor cortisol supplementation is therefore not consensual.

Conclusion

Optimization of the quality of kidney grafts starts at the phase of donor conditioning. This optimization must be based on knowledge of the pathophysiological processes occurring after brain death in order to set up pharmacological strategies designed to maintain kidney perfusion and oxygenation. Pharmacological strategies designed to prevent ischemia-reperfusion injury must start with the donor by control of the endocrine and autonomic storm induced by brain death.

Disclosure of interest

J. Branchereau: Conferences: attendance as audience member (cost of travel and accommodation paid for by an organisation or company), (IGL).

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