

REVIEW

## Ketamine and Peripheral Inflammation

Marc De Kock,<sup>1</sup> Sebastien Loix<sup>2</sup> & Patricia Lavand'homme<sup>1</sup>

<sup>1</sup> Department of Anesthesia, Perioperative Medicine, Institute of Neurosciences, Catholic University of Louvain, Brussels, Belgium

<sup>2</sup> Intensive care unit, Jolimont Hospital, La Louvière, Belgium

### Keywords

Immune system; Inflammation; Ketamine; Peripheral.

### Correspondence

Marc De Kock, M.D., Ph.D., Department of Anesthesia, Clin Univ St Luc, 10-1821 av Hippocrate, 1200 Brussels, Belgium.

Tel.: +32-2-7641821;

Fax: +32-2-7643699;

E-mail: marc.dekock@uclouvain.be

Received 29 November 2012; revision

1 March 2013; accepted 1 March 2013.

### SUMMARY

The old anesthetic ketamine has demonstrated interactions with the inflammatory response. This review intends to qualify the nature and the mechanism underlying this interaction. For this purpose, preclinical data will be presented starting with the initial works, and then, the probable mechanisms will be discussed. A summary of the most relevant clinical data will be presented. In conclusion, ketamine appears as a unique “homeostatic regulator” of the acute inflammatory reaction and the stress-induced immune disturbances. This is of some interest at a moment when the short- and long-term deleterious consequences of inadequate inflammatory reactions are increasingly reported. Large-scale studies showing improved patient’s outcome are, however, required before to definitively assert the clinical reality of this positive effect.

doi: 10.1111/cns.12104

### Introduction

This work will focus on the effects of ketamine on peripheral inflammation. This old anesthetic is a particular substance characterized by interactions with numerous receptor systems. For example, it is best known as a competitive antagonist of the excitatory neurotransmission (*N*-methyl-D-aspartate NMDA receptor, Nr2b subtype) [1]. It is able to recruit the catecholaminergic, cholinergic and opioid systems [2,3]. It acts directly on some ionic channels receptors (Na<sup>+</sup>, Ca<sup>++</sup>) [4] and is ligand at the sigma receptors and the trace amine-associated receptors (*N,N*-Dimethyltryptamine, 5-methoxy-*N,N*-dimethyltryptamine) [5]. These multiple interactions probably account for its various clinical effects such as anesthesia, analgesia, antihyperalgesia, induction of psychiatric symptoms compatible with schizophrenia, or positive effects on depressive mood [6,7]. Moreover, it is known that ketamine influences the immune system particularly the inflammatory reaction an immune response that largely derives from activation the “innate” immune mechanisms. A close consideration of this property is of particular interest at a moment where successful completion of the inflammatory reaction appears as an important determinant for positive outcome in patients undergoing surgery or critical care patients [8,9]. In this field, ketamine appears as a unique homeostatic regulator of the acute inflammatory reaction and the stress-induced immune disturbances. This review intends to qualify the nature and the mechanism underlying this interaction. For this purpose, preclinical data will be

presented starting with the initial works demonstrating a ketamine/immune interaction, and then, the probable mechanisms will be discussed. Finally, a summary of the most relevant clinical data will be presented.

### A “Successful” Inflammatory Reaction

Inflammatory reaction is capital for the maintenance of body homeostasis and survival [10]. Its role is to fight infection and tissue injury by promoting healing. It is based on multiple step reactions each under the influence of several positive (pro-inflammatory) or negative (anti-inflammatory) retro-controls. On this fine tuning, depends on the success of this reaction, it is noteworthy that an inadequate inflammatory response either excessive or insufficient is deleterious for the organism [11].

To make an overcomplicated story short, the critical steps of the inflammatory reaction may be summarized as follows:

This reaction is triggered when the resident innate immune or immune-assimilated cells such as macrophages, fibroblasts, mast cells, and dendritic cells or circulating leucocytes detect pathogen invasion or cell damage [12]. Detection mechanisms involve intracellular and surface-expressed pattern recognition receptors, that is, the Toll receptors (TLRs) that have a central role to activate innate immunity [13–16]. As a consequence of the reaction initiated, transcription factors (NF-κB, AP1, CREB, c/EBP, and IRF) will be activated. Accordingly, genes encoding for cytokines, chemokines, adhesion molecules and regulators of the extracellu-

lar matrix will be expressed [17]. At this moment, the inflammatory reaction become florid, circulating leukocytes are recruited to the region. In this regard, alterations of the vascular walls close to the site are of primary importance. Mediators such as histamine, prostaglandins and nitric oxide cause local vasodilation which increase blood flow and the amount of recruited leukocytes. Under the influence of histamine and leukotrienes, vascular permeability is increased allowing plasma proteins and leukocytes to exit the circulation. Additionally, the released cytokines (TNF, IL-1) promote the leukocytes extravasation. All the immune-competent cells present at the site of infection or injury will remove foreign bodies and injured materials by phagocytosis. At the same time, they release cytokines and other mediators that will shape the adaptative immune response and initiate the active process of inflammation resolution and healing.

As previously mentioned, the inflammatory reaction is a highly regulated process [18]. This is mandatory because it is potentially so potent that it can definitively disrupt the homeostasis and compromise survival. The regulation of this reaction occurs at two levels: a local and a central one. At the local level: very early, anti-inflammatory cytokines (i.e., IL-1receptor antagonist, IL-4, IL-10, Interferon  $\alpha$ ), are released by the immune cells that oppose to the action of the inflammatory ones (i.e., IL-1, IL-6, TNF- $\alpha$ ) by promoting, among others, the early apoptosis of the inflammatory cells [14]. Lipid mediators are other important actors in the active resolution process. At the moment of aggression (viral, bacterial, tissue destruction) under the influence of the COX-2 enzyme, pro-inflammatory lipid mediators are released such as arachidonic acid-derived leukotrienes and prostaglandins. At a particular moment and under not yet exactly known influences (reduction of inflammatory cells, release of pro-inflammatory cytokines), using the same COX-2 enzyme, the host will shift to the synthesis of lipid mediators active in the resolution, that is, the lipoxins, resolvins, and protectins [19–21].

At the central level, during peripheral inflammation, it is noteworthy that there exist bilateral communication between the immune and the nervous systems. The central nervous system (CNS) is informed that “something” is happening in the periphery by the peripheral nervous system and by the immune system (i.e., glial hyperactivity consecutive to peripheral inflammation [22]). It will adapt behavior and physiologic responses to maintain homeostasis during this stress situation. Additionally, the CNS exerts a potent modulatory action on the inflammation through efferent hormonal (the hypothalamo-pituitary axis [HPA]) and the autonomic neuronal pathways both sympathetic (noradrenergic nerves) and parasympathetic (the vagus nerve) [23]. This is done to keep the inflammatory reaction as local as possible and locally as efficient as possible. The immune translation of this is best described as a predominance of the Th2 (anti-inflammatory) upon the Th1 (pro-inflammatory) type of reaction. Nevertheless, excessive decrement of Th1/Th2 ratio by exaggerated repression of the Th1 type of reaction is also particularly deleterious for the organism. This state of “immunoparalysis” is associated with increased mortality and complications rates (i.e., secondary infections) [8,11,24]. Consequently, to maintain an adequate equilibrium between pro- and anti-inflammatory influences is of critical importance for a successful recovery after an inflammatory challenge.

## Ketamine as a “Regulator” of the Inflammatory Reaction: Preclinical Studies

### Direct Effect on the Local Effectors of the Inflammatory Reaction

#### Which Steps of the Inflammatory Reaction are Concerned by Ketamine?

The notion that ketamine interferes with immunity comes from the early observations of improved outcome in critically ill patients [25] and in experimental septic shock [26]. This prompted numerous laboratory investigations to uncover the mechanisms accounting for this beneficial effect [27–31].

To summarize all these works, we can state that ketamine is able to regulate the local inflammatory process very early in its course by direct action on the key players of the innate immunity (Table 1). Ketamine affects the functioning of numerous cellular effectors of the inflammatory reaction. The first investigations have focused mainly on the production of cytokines by immune cells consecutive to an inflammatory challenge. Results obtained after these *in vitro* and/or *ex vivo* experimentations clearly demonstrate that ketamine significantly reduces the amount of pro-inflammatory cytokines without affecting the production of the anti-inflammatory ones. In other words, ketamine helps to avoid exacerbated pro-inflammatory reaction [32–37]. Two findings deserve attention. First: ketamine has no effect on the immune cells producing inflammatory cytokines in the absence of an inflammatory stimulus. Second, its regulatory action is more pronounced when this drug is administered before the inflammatory challenge [36]. This is of particular interest knowing that ketamine is mostly given at the induction of anesthesia before surgery.

Early experimental studies have mainly focused on cytokines production because it was, at that time, an inflammatory marker easy to measure. Inflammatory reaction is also under the influence of other soluble mediators such as chemokines and various growth factors released by the effector cells. At the present time, little is known about any specific effect of ketamine on these types of inflammatory mediators. In contrast, other modulatory effects of ketamine on specific actions of the inflammatory cells are described [38–42]. For example, the oxidative potency and NO production by the macrophages are reduced [32,43]. The effect of ketamine on NO production deserves some attention: Nitric oxide acts as a mediator and an effector of the inflammatory reaction. Nitric oxide is cytotoxic on the microorganisms and the tumor cells. Its production is under the dependence of the inducible form of NO synthase (iNOS) which is stimulated by pro-inflammatory cytokines [44,45]. The inhibition produced by ketamine is time- and dose-dependent. Interestingly, it is not an NMDA-related property because another NMDA antagonist (MK-801) failed to decrease NO production. Inflammation-induced NO production reduces the release of pro-inflammatory cytokines by immune competent cells [46,47]. It is part of the multiple feedback loops aiming to regulate the inflammatory reaction. These apparently contradictory effects of ketamine perfectly illustrate its immune “regulatory” properties. In fact, this drug reduces the production of NO, this is an anti-inflammatory effect and consequently

**Table 1** Summary of the early experimentation demonstrating an “anti-inflammatory” effect of ketamine

Conditions	Endpoints	Results: inflammatory	Results: others	Additional informations	References
<i>In vivo</i> Rats + lipopolysaccharides (LPS)	TNF- $\alpha$ MABP Acidosis	↓ TNF- $\alpha$	↓ Acidosis ↓ Hepatic insult ↑ Survival		27
Ketamine IM 100 mg/kg	Hepatic insult Survival				
<i>In vivo</i> Rats + <i>Escherichia coli</i>	TNF- $\alpha$ IL-6	↓ TNF- $\alpha$ ↓ IL-6	↑ Survival		28
Ketamine IP 50 mg/kg	Survival				
<i>In vivo</i> Rats + <i>E. coli</i> + Burns	IL-6 Survival	↓ IL-6	↑ Survival		29
Ketamine IP 10 mg/kg					
<i>In vivo</i> Rats + Burns	Survival		↑ Survival In comparison with midazolam/fentanyl anesthesia	Heat shock response improved	30
Ketamine “anesthetic dose”					
<i>In vivo</i> Rats + <i>E. coli</i>	Acidosis Survival		↓ Acidosis ↑ Survival	Effects at 10 mg/kg	31
Ketamine IV Dose/response curve 3 doses 5, 10 and 20 mg/kg					
<i>In vivo</i> Rats + <i>E. coli</i>	IL-6/IL-10	Ratio improved		Better than propofol	34
Ketamine IV 10 mg/kg/h					
<i>In vivo</i> Rats + <i>E. coli</i>	TNF- $\alpha$ IL-6	↓ TNF- $\alpha$ ↓ IL-6	↑ Survival	Preventive effect Curative effect: less pronounced but still present	36
Ketamine IV 10 mg/kg/h	Acidosis Survival				
<i>In vitro</i> Peritoneal macrophages of mice + LPS and ketamine	TNF- $\alpha$	↓ TNF- $\alpha$			33
<i>In vitro</i> Human whole blood + LPS	TNF- $\alpha$ IL-6, IL-8	↓ TNF- $\alpha$ ↓ IL-6, IL-8	Concentrations ≥ 20 $\mu$ g/mL ≥ 100 $\mu$ g/mL	No effect if no immunostimulation	32
<i>In vitro</i> Human whole blood + Staph endotoxin	TNF- $\alpha$ IL-6, IL-8	↓ TNF- $\alpha$ ↓ IL-6 ↓ IL-8	Concentrations ≥ 50 $\mu$ M ≥ 100 $\mu$ M ≥ 500 $\mu$ M	Both ketamine isomers are immune active	35
<i>In vitro</i> Equine Macrophages cell lines + LPS	TNF- $\alpha$ IL-6	↓ TNF- $\alpha$ ↓ IL-6	Concentrations ≥ 1.8 $\mu$ M ≥ 1.8 $\mu$ M		37
Ketamine concentrations 0, 0.36, 1.8, 3.6, 18, 36 $\mu$ M					
<i>In vitro</i> Human whole blood + LPS	TNF- $\alpha$ IL-1 $\beta$	↓ TNF- $\alpha$ ↓ IL-1 $\beta$		Original effect of ketamine compared with midazolam, thiopental, fentanyl	42
Ketamine concentrations 5.8910 <sup>-5</sup> M					

suppresses the NO-induced inhibition of pro-inflammatory cytokines production, a pro-inflammatory effect.

Additionally, ketamine significantly limits the diapedesis of the neutrophils to the site of inflammation [48–50]. The underlying mechanism appears to be a reduction in adhesion molecules

expressed on the surface of the immune cell [51] and not an interaction with the inflammatory endothelial function [48]. This is of some interest because preservation of an intact endothelial function is correlated with positive outcome after ischemia/reperfusion injury [52]. These observations do not exclude any action of

ketamine on the other determinants of inflamed tissue penetration of leukocytes (i.e., chemokines as suggested by the work of Dhote et al. in the CNS [53]) but no specific data can be found in the literature.

Recently attention was drawn on a particular population of cytotoxic lymphocytes: the Natural Killer (NK) cells. These are a major component of the innate immunity. They significantly contribute to the first line defense against viral infection and tumor cells growth [54]. Consequently, impairment of their cytotoxic properties, for example, in the perioperative period, is suspected to favor postoperative infections and metastatic cancer cells proliferation in the case of surgery for the resection of a primary tumor. It is known that opioids used as ketamine during anesthesia potentially reduce NK activity *in vitro*. In contrast, ketamine did not significantly affect the functioning of NK cells [55].

Finally, ketamine favor the resolution of inflammation by precipitating the apoptosis of the inflammatory cells [56]. The active process of resolution involves several cellular mechanisms. Among these, the clearance of inflammatory cells is of critical importance [57]. This is obtained both by apoptosis (cell suicide) and/or egress from the tissues. Once again, the regulatory effect of ketamine has to be noted. On the one hand, it promotes apoptosis by specific mitochondrial pathway in human lymphocytes [56], and on the other; it reduces the release by the inflammatory cells of the pro-inflammatory cytokine TNF- $\alpha$ , the major activator of the apoptotic pathways [58]. This is another example of ketamine being a regulator of inflammation, having sometimes opposite effects.

### By Which Mechanisms Ketamine Interferes with the Local Inflammatory Reaction?

As evidenced previously, ketamine shows pleiotropic anti-inflammatory effects. This is a strong argument for a very early interaction in the time-course of the inflammatory cascade. In this regard, more precise idea on the mechanisms involved are to be found in the repression of the nuclear factor NF $\kappa$ -b [59,60]. The NF $\kappa$ -b is an intracellular protein that activates the transcription of genes coding for cytokines in immune competent cells. It is a key transcriptional regulator playing a central role in the onset of inflammation [61]. How is this factor controlled? Typically, the NF $\kappa$ -b is activated by prototype inflammatory mediators such as IL-1 $\beta$  and TNF $\alpha$  [62] released by the resident immune cells facing an inflammatory stimulus. Other regulators are described such as the adenosine receptors system [63] and the recently described Wnt5a-signaling pathways.

By which of these mechanisms ketamine is acting?

First: *the release of the prototype inflammatory mediators*. Some experimental works using a rodent model of endotoxic shock suggests that ketamine may interfere with the early detection mechanisms such as the Toll-like receptors (TLRs) [64,65]. The fact that ketamine is able to interact with TLR-derived mechanisms is of some interest. Remember that most of the *in vitro* anti-inflammatory properties of ketamine were demonstrated using a lipopolysaccharides (LPS) challenge. These LPS are a major constituent of gram negative bacteria and are recognized as specific agonists of the TLRs type 4.

Whether the interaction of ketamine with TLR-derived mechanisms is the consequence of antagonism at NMDA receptor system is not yet determined. Nevertheless, it is firmly established that the NMDA glutamergic transmission system participate directly to the inflammatory cascade and its consequences, that is, pain by mechanisms including peripheral nerve, spinal cord sensitization, glial activation and dorsal root reflexes [66–69].

Second: *the adenosine receptor system*. Adenosine is a metabolite of adenosine triphosphate (ATP). This purine nucleoside has been described as a “retaliatory metabolite” because of its ability to function in an autocrine manner and to modify the activity of a wide range of cells following its extracellular accumulation during cell stress or injury. To summarize its actions, it functions as a local homeostatic modulator by interacting with four cell surface receptors (A1, A2a, A2b, A3) [70]. The A2a receptors are mainly involved in the modulation of inflammatory and immune responses. Their critical role is to maintain tissue integrity by down-regulating phlogistic reactions, repression of the synthesis of pro-inflammatory cytokines, inhibition of neutrophil adhesion, degranulation and anti-oxidant activity [71]. Mazar and coworkers [72] demonstrated that the ketamine-induced anti-inflammatory effects (including the inhibition of the NF $\kappa$ -b [73]) also result from the activation of this endogenous A2a-mediated homeostatic protector system [74]. Interesting to point out, ketamine interferes with the functioning of the COX-2 enzyme through recruitment of the adenosine 2a receptor system altering the production of lipid inflammatory mediators without affecting the lipid-induced resolution process [75–77]. There is, however, at the present time, no evidence that ketamine experimentally promotes the active resolution process.

Third: NMDA receptors activation was recently demonstrated to directly activate *Wnt5a signaling pathways*, a “nonclassical” activator of the NF $\kappa$ -b [78]. Consequently, ketamine blocks this alternative route recognized as critical for endothelium activation during inflammation [79].

Finally, several other mechanisms are described that participates to the anti-inflammatory effects of ketamine. For example, ketamine interacts directly with some *ion channels* such as the large conductance Ca<sup>++</sup>-activated K<sup>+</sup> channels. Although no direct action on peripheral inflammation were reported, blockade of these channels is demonstrated to prevent the inflammatory signals arising from the periphery to activate the microglia by suppressing the pro-inflammatory cytokines production of the immune cells in the CNS. The dose used in this experimentation were, however, particularly high [4]. Moreover, ketamine activates another important anti-inflammatory pathway, the heme oxygenase enzyme system. The anti-inflammatory properties of this system are secondary to the production of metabolites generated during the catabolism of heme. These include biliverdin, free iron, and CO. This system provides powerful protective effects during sepsis and ischemia/reperfusion insults [80]. To which extent these mechanisms account for the inflammatory “protective” effects of ketamine remains to be elucidated.

## Effects of Ketamine on the Systemic Regulators of the Inflammatory Reaction

Facing a localized inflammatory process, the organism will react by promoting a systemic protective anti-inflammatory effect. In other words, a predominance of the Th2 (anti-inflammatory) upon the Th1 (pro-inflammatory) type of reaction will be observed. Does ketamine interfere with this important immune ratio? Experimental *in vitro* data using CD4-positive lymphocytes separated from healthy volunteers clearly show that ketamine used at concentration of 10  $\mu\text{g}/\text{mL}$  (a concentration comparable with the one obtained after an IV bolus of 0.5 mg/kg) significantly increased the Th1/Th2 ratio and might consequently be benefit to the patient's global immune function [81]. In comparison with morphine (used in the same model at human analgesic concentration), both drugs reduce the rate of Th cell differentiation and subsequent cytokines production simulation. However, morphine potently decreases the Th1/Th2 ratio in comparison with ketamine [82].

In contrast with the above-described effect on Th1/Th2 differentiation, ketamine may potentially participate to the stress reaction-induced anti-inflammatory effect (Th-1 repression). These are consecutive to the activation of the sympathetic system and the HPA resulting in increased adrenal activity and corticosteroid production. Studies on human volunteers clearly show that ketamine stimulates both systems [83,84]. Nevertheless, no data are available on the possible immune consequences of this interaction.

Ketamine promotes potentially both anti- and pro-inflammatory reactions. In this regard, it has to be considered more as a regulator, a drug that promotes immune homeostasis during stress conditions. This is exemplified by the following observation: Ketamine used for recreational purposes is often associated with cocaine. Cocaine stimulates ACTH and cortisol production resulting in an exacerbated systemic anti-inflammatory effect. When ketamine is associated with cocaine in an animal model of addiction, the cocaine-induced surge in ACTH and cortisol is blunted by ketamine promoting in this particular circumstance a pro-inflammatory effect [85,86].

## Ketamine as a "Regulator" of the Inflammatory Reaction: Clinical Evidence

Ketamine is regularly used in the perioperative period for anesthetic (high doses 2–3 mg/kg IV bolus) or more recently for anti-hyperalgesic purposes (low dose 0.5–0.25 mg/kg IV bolus). Surgery implies tissue destruction and elicits a significant inflammatory reaction. Is ketamine given before and/or during surgery associated with a more adequate inflammatory reaction and consequently a more favorable postoperative outcome?

In patients undergoing cardiac surgery under extracorporeal circulation (ECC) (a circumstance known to strongly activate the inflammatory cascade), the administration of a single IV low dose of ketamine (0.25 mg/kg) at induction of anesthesia significantly reduced the production of IL-6 a pro-inflammatory cytokine. Interesting to note this reduction was still present at the seventh postoperative day, long time after ketamine has disappeared from patients' blood [87]. Bartoc and coworkers reproduced this

observation in patients receiving an IV bolus of ketamine (either 0.25 or 0.5 mg/kg) at induction of the anesthesia. These authors reported reduced biological inflammatory markers (IL-6 in both ketamine groups at arrival in the ICU. C-reactive protein and IL-10 only in the 0.5 mg/kg group at the first postoperative day) when compared to the placebo group. Interestingly, patients treated with ketamine presented with less post ECC vasoplegia during the entire observation period [88]. Another study conducted in a pediatric cardiac surgery population failed to demonstrate any anti-inflammatory action of ketamine after ECC. The administration of steroids in both the control and the ketamine groups probably explains this negative result [89]. In patients undergoing liver transplantation, ketamine administration was associated with reduced levels of circulating TNF- $\alpha$  and IL-6 [90].

A recent meta-analysis by Dale *et al.* [91] considered the effects of ketamine on IL-6 production in patients undergoing surgery. Concentrations of this major pro-inflammatory cytokine were used as a biomarker of the inflammatory reaction. Of the 14 studies eligible for evaluation (684 patients from cardiopulmonary bypass operations, abdominal, thoracic and cataract surgeries), six studies (331 patients) were included in the meta-analysis. It was concluded that ketamine, given at an IV bolus dose of at least 0.15 mg/kg before surgery significantly inhibits the early postoperative IL-6 inflammatory response. This effect is at least as important as the one obtained after pre-treatment with one of the most potent anti-inflammatory medication, that is, methylprednisolone (30 mg/kg) in cardio-pulmonary bypass surgery [92]. Nevertheless, the effect of methylprednisolone was short-lived (approximately 1 h) in comparison with ketamine where durations of up to 6 h were documented [91].

Although there is no study that specifically considers clinical outcome, it is supposed to be improved. Indeed, elevated levels of IL-6 in the postoperative period were regularly reported to be associated with poor outcome [93–95].

Another way to get some information about the consequences of immune regulatory properties of the ketamine is to consider the effects of this drug on the deleterious postoperative events usually ascribed to exacerbated pro-inflammatory reactions.

## Hyperalgesia

Ketamine alleviates postoperative pain syndrome related to exaggerated pro-inflammatory reaction. Ketamine significantly reduces trauma-induced hyperalgesia, a phenomenon that can be ascribed to both its NMDA antagonist effect and its anti-inflammatory properties. Positive consequences were noted on the development of chronic postsurgical pain in limited series of patients [6,96–98].

Moreover, ketamine is highly efficient to prevent opiate-induced hyperalgesia. This action is usually ascribed to the blockade of excitatory (NMDA) transmission induced by the activation of  $\mu$ -opiate excitatory receptors [99]. Nevertheless, some data support the involvement of inflammatory mechanisms in opiate-induced analgesia. It is demonstrated, for example, that glia can exhibit pro-inflammatory responses to opioids, contributing to opioid-induced hyperalgesia and the development of tolerance and dependence [100]. Interestingly, the mechanism contributing to opioid-induced pro-inflammatory actions is probably the

activation by the opioids of the TLR-4 receptors system [101]. It may explain why a drug such as ketamine that reduces the activation of the TLR-4 opposes to the pro-inflammatory effects of the opioids and reduce opioid-induced hyperalgesia.

## Postoperative Cognitive Dysfunction

Postoperative cognitive dysfunction is a complication following surgery and particularly cardiac surgery. It was observed that patients undergoing cardiac procedures where ketamine was associated (on iv bolus of 0.5 mg/kg at induction of anesthesia) presented a significantly reduced incidence of this complication compared with controls as assessed by improved recent verbal and nonverbal memories and executive functions at 1 week after surgery. Additionally, the inflammatory marker CRP was significantly reduced in the ketamine group [102]. The exact mechanisms underlying postoperative cognitive dysfunctions are not fully understood [103]. Nevertheless, the inflammatory reaction consecutive to the surgical trauma is incriminated. Peripheral inflammatory cytokines can takes effects on the CNS. This occurs directly, cytokines bind their receptors in the CNS and activate microglial cells but also indirectly by activation of vascular endothelial cells. Indeed, perioperative increased levels of CRP and inflammatory cytokines are associated with the occurrence of postoperative cognitive dysfunction in patients undergoing

surgery under ECC [104]. Consequently, it can be hypothesized that the inflammatory regulatory properties of ketamine this positive effect on postoperative outcome. Interestingly, a recent experimental study by Wang et al. [105] pointed out a probable link between activation of TLR-4 signaling on microglia and postoperative cognitive dysfunction.

## Conclusions

Ketamine appears as a drug promoting the inflammatory homeostasis. Locally, ketamine interferes very early on the determinants of primary immunity. It prevents the exacerbation and the extension of local inflammation without blunting the local process and delaying inflammatory resolution. Ketamine also prevents the general anti-pro-inflammatory mechanisms to excessively overcome the pro-inflammatory influences. In other words, ketamine is immunomodulatory rather than immunosuppressive. These quite interesting properties deserve, however, confirmation in large prospective human studies considering not only some inflammatory markers but also clinical outcome parameters.

## Conflict of Interest

The authors declare no conflict of interest.

## References

- Zhuo M. Plasticity of NMDA receptor NR2B subunit in memory and chronic pain. *Mol Brain* 2009;**2**:4.
- Scheller M, Bufler J, Hertle I, et al. Ketamine blocks currents through mammalian nicotinic acetylcholine receptor channels by interaction with both open and closed state. *Anesth Analg* 1996;**83**:830–836.
- Smith D, Pekoe G, Martin L, Coalgate B. The interaction of ketamine with the opiate receptor. *Life Sci* 1980;**26**:789–799.
- Hayashi Y, Kawaji K, Sun I, et al. Microglia Ca (2+)-activated K (+) channels are possible molecular targets for the analgesic effects of S-ketamine on neuropathic pain. *J Neurosci* 2011;**31**:17370–17382.
- Wallach JV. Endogenous hallucinogens as ligands of the trace amine receptor: a possible role in sensory perception. *Med Hypotheses* 2009;**72**:91–94.
- De Kock M, Lavand'homme P, Waterloos H. Balanced analgesia in the perioperative period: is there a place for ketamine. *Pain* 2001;**92**:373–380.
- Zarate CA, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry* 2006;**63**:856–864.
- Kimura F, Shimizu H, Yoshidome H, et al. Immunosuppression following surgical and traumatic injury. *Surg Today* 2010;**12**:793–808.
- Marik PE, Flemmer M. The immune response to surgery and trauma: implications for treatment. *J Trauma Acute Care Surg* 2012;**73**:801–808.
- Selye H. Forty years of stress research: principal remaining problems and misconceptions. *Can Med Assoc J* 1976;**115**:53–56.
- Hirsiger S, Simmen H-P, Werner C, Wanner G, Rittirsch D. Danger signals activating the immune response after trauma. *Mediators Inflamm* 2012;**2012**:315941.
- Newton K, Dixit V. Signalling in Innate Immunity and inflammation. *Cold Spring Harb Perspect Biol* 2012;**4**:a006049.
- Kawai T, Akira S. TLR signaling. *Semin Immunol* 2007;**19**:24–32.
- Wagner H. Endogenous TLR ligands and autoimmunity. *Adv Immunol* 2006;**91**:159–173.
- Kaisho T, Akira S. Toll-like receptor function and signaling. *J Allergy Clin Immunol* 2006;**117**:979–987.
- Arumugam TV, Okun E, Tang S-C, et al. Toll-like receptors in ischemia-reperfusion injury. *Shock* 2009;**32**:4–16.
- Suntharalingam G, Perry MR, Ward S, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *NEJM* 2006;**355**:1018–1028.
- Johnston GR, Webster NR. Cytokines and the immunomodulatory function of the vagus nerve. *Br J Anaesth* 2009;**102**:453–462.
- Kohli P, Levy B. Themed section: mediators and receptors in the resolution of inflammation. Review: resolvins and protectins: mediating solutions to inflammation. *Br J Pharmacol* 2009;**158**:960–971.
- Weylandt KH, Chiu CY, Gomolka B, et al. Omega-3 fatty acids and their lipid mediators: towards an understanding of resolving and protectin formation. Omega-3 fatty acids and their resolving/protectin mediators. *Prostaglandins Other Lipid Mediat* 2012;**97**:73–82.
- Levy BD, Clish CB, Schmidt B, Gronert K, Serhan CN. Lipid mediator class switching during acute inflammation: signals resolution. *Nat Immun* 2001;**2**:612–619.
- Milligan E, Watkins LR. Pathological and protective role of glia in chronic pain. *Nat Rev Neurosci* 2009;**10**:23–36.
- Waldburger JM, Firestein GS. Regulation of peripheral inflammation by the central nervous system. *Curr Rheumatol Rep* 2010;**12**:370–378.
- Muenzer JT, Davis CG, Schmidt RE, Dunne WM, Coopersmith CM, Hotchkiss RS. Characterization and modulation of the immunosuppressive phase of sepsis. *Infect Immun* 2010;**78**:1582–1592.
- Yli-Hankala A, Kileurvera M, Randell T, et al. Ketamine anesthesia in patients with septic shock. *Acta Anaesthesiol Scand* 1992;**36**:483–485.
- Vanderlinden P, Gilbert E, Engelman E, et al. Comparison of halothane, isoflurane, alfentanil, and ketamine in experimental septic shock. *Anesth Analg* 1990;**70**:608–613.
- Koga K, Ogata M, Takenaka I, Matsumoto T, Shigematsu A. Ketamine suppresses TNF-alpha activity and mortality in carrageenan-sensitized endotoxin shock model. *Circ Shock* 1994;**44**:160–168.
- Shaked G, Czeiger D, Dukhno O, et al. Ketamine improves survival and suppresses IL-6 and TNF alpha production in a model of Gram-negative bacterial sepsis in rats. *Resuscitation* 2004;**62**:237–242.
- Gurfinkel R, Czeiger D, Douvdevani A, et al. Ketamine improves survival in burn injury followed by sepsis in rats. *Anesth Analg* 2006;**103**:392–402.
- Neder Meyer T, Lazaro da Silva A. Ketamine reduces mortality of severely burnt rats, when compared to midazolam plus fentanyl. *Burns* 2004;**30**:425–430.
- Taniguchi T, Takemoto Y, Kanakura H, Kidani Y, Yamamoto K. The dose related effect of ketamine on mortality and cytokine responses to endotoxin-induced shock in rats. *Anesth Analg* 2003;**97**:1769–1772.
- Kawasaki T, Ogata M, Kawasaki C, et al. Ketamine suppresses proinflammatory cytokine production in human whole blood in vitro. *Anesth Analg* 1999;**89**:665–669.
- Takenaka I, Ogata M, Koga K, Matsumoto T, Shigematsu A. Ketamine suppresses endotoxin-induced tumor necrosis factor alpha production in mice. *Anesthesiology* 1994;**80**:402–428.
- Taniguchi T, Kanakura H, Takemoto Y, Kidani Y, Yamamoto K. Effects of ketamine and propofol on the ratio of interleukin-6 to interleukin-10 during endotoxemia in rats. *Tohoku J Exp Med* 2003;**200**:85–92.
- Kawasaki C, Kawasaki T, Ogata M, Nandate K, Shigematsu A. Ketamine isomers suppress

- superantigen-induced proinflammatory cytokine production in human whole blood. *Can J Anaesth* 2001;**48**:819–823.
36. Taniguchi T, Shibata K, Yamamoto K. Ketamine inhibits endotoxin-induced shock in rats. *Anesthesiology* 2001;**95**:928–932.
  37. Lankveld DPK, Bull S, Van Dijk P, Fink-Gremmels J, Hellebrekers LJ. Ketamine inhibits LPS-induced TNF- $\alpha$  and interleukin-6 in an equine macrophage cell line. *Vet Res* 2005;**36**:257–262.
  38. Chang Y, Chen TL, Sheu JR, Chen RM. Suppressive effects of ketamine on macrophage functions. *Toxicol Appl Pharmacol* 2005;**204**:27–35.
  39. Pekoe GM, Peden D, Van Dyke K. Impairment of leukocyte myeloperoxidase bactericidal mechanisms with ketamine. *Agents Actions* 1983;**13**:59–62.
  40. Zilberstein G, Levy R, Rachinsky M, et al. Ketamine attenuates neutrophil activation after cardiopulmonary bypass. *Anesth Analg* 2002;**95**:531–536.
  41. Krumholz W, Endrass J, Hempelmann G. Inhibition of phagocytosis and killing of bacteria by anaesthetic agents in vitro. *Br J Anaesth* 1995;**75**:66–70.
  42. Larsen B, Hoff G, Willhelm W, Buchinger H, Wanner G, Bauer M. Effect of intravenous anesthetics on spontaneous and endotoxin-stimulated cytokine response in cultured human whole blood. *Anesthesiology* 1998;**89**:1218–1227.
  43. Yang J, Li W, Duan M, et al. Large dose ketamine inhibits lipopolysaccharide-induced acute lung injury in rats. *Inflamm Res* 2005;**54**:133–137.
  44. Li CY, Chou TC, Wong CS, et al. Ketamine inhibits nitric oxide synthase in lipopolysaccharide-treated rat alveolar macrophages. *Can J Anaesth* 1997;**44**:989–995.
  45. Shimaoka M, Iida T, Ohara A, et al. Ketamine inhibits nitric oxide production in mouse-activated macrophage-like cells. *Br J Anaesth* 1996;**77**:238–242.
  46. Kelleher ZT, Matsumoto A, Stamler JS, Marshall HE. NOS2 regulation of NF- $\kappa$ B by S-nitrosylation of p65. *J Biochem* 2007;**24**:1412–1420.
  47. Kim F, Huri DA, Snyder SH. Inducible nitric oxide synthase binds, S-nitrosylates, and activates cyclooxygenase-2. *Science* 2005;**310**:1966–1970.
  48. Zahler S, Heindl B, Becker BF. Ketamine does not inhibit inflammatory responses of cultured human endothelial cells but reduces chemotactic activation of neutrophils. *Acta Anaesthesiol Scand* 1999;**43**:1011–1016.
  49. Hofbauer R, Moser D, Hammerschmidt V, Kapiolis S, Frass M. Ketamine significantly reduces the migration of leukocytes through endothelial cell monolayers. *Crit Care Med* 1998;**26**:1545–1549.
  50. Schmidt H, Ebeling D, Bauer H, et al. Ketamine attenuates endotoxin-induced leukocyte adherence in rat mesenteric venules. *Crit Care Med* 1995;**23**:2008–2014.
  51. Weigand M, Schmidt H, Zhao Q, Plaschke K, Martin E, Bardenheuer HJ. Ketamine modulates the stimulated adhesion molecule expression on human neutrophils in vitro. *Anesth Analg* 2000;**90**:206–212.
  52. Qi XL, Nguyen TL, Andries L, Sys SU, Rouleau JR. Vascular endothelial dysfunction contributes to myocardial depression in ischemia-reperfusion in the rat. *Can J Physiol Pharmacol* 1998;**76**:35–45.
  53. Dhote F, Carpentier P, Barbier L, et al. Combinations of ketamine and atropine are neuroprotective and reduce neuroinflammation after toxic status epilepticus in mice. *Toxicol Appl Pharmacol* 2012;**259**:195–209.
  54. Orange JS, Ballas ZK. Natural killer cells in human health and disease. *Clin Immunol* 2006;**118**:1–10.
  55. Forget P, Collet V, Lavand'homme P, De Kock M. Does analgesia and condition influence immunity after surgery? Effects of fentanyl, ketamine and clonidine on natural killer cell activity at different ages. *Eur J Anaesthesiol* 2010;**27**:233–240.
  56. Braun S, Gaza N, Werdehausen R, et al. Ketamine induces apoptosis via mitochondrial pathway in human lymphocytes and neuronal cells. *Br J Anaesth* 2010;**105**:347–354.
  57. Rossi AG, Sawatzky DA, Walker A, et al. Cyclin kinase inhibitors enhance the resolution of inflammation by promoting inflammatory cells apoptosis. *Nat Med* 2006;**12**:1056–1064.
  58. Perl M, Chung CS, Ayala A. Apoptosis. *Crit Care Med* 2005;**33**:s526–s528.
  59. Sakai T, Takashi I, Whitten CW, Giesecke AH, Lipton JM. Ketamine suppresses endotoxin-induced NF- $\kappa$ B expression. *Can J Anaesth* 2000;**47**:1019–1024.
  60. Sun J, Wang D, Liu H, Xu JG. Ketamine suppresses endotoxin-induced NF- $\kappa$ B activation and cytokines production in the intestine. *Acta Anaesth Scand* 2004;**48**:317–321.
  61. Bonizzi G, Karin M. The two NF- $\kappa$ B activation pathways and their role in innate and adaptive immunity. *Trends Immunol* 2004;**25**:280–288.
  62. Perkins N. Integrating cell-signalling pathways with NF- $\kappa$ B and IKK function. *Nat Rev Mol Cell Biol* 2007;**8**:49–62.
  63. Hasko G, Cronstein BN. Adenosine: an endogenous regulator of innate immunity. *Trends Immunol* 2004;**25**:33–39.
  64. Yu M, Shao D, Feng X, Duan M, Xu J. Effects of ketamine on pulmonary Tlr4 expression and NF- $\kappa$ B activation during endotoxemia in rats. *Methods Find Exp Clin Pharmacol* 2007;**29**:395–399.
  65. Yu M, Shao D, Liu J, Zhu J, Zhang Z, Xu J. Effects of ketamine on levels of cytokines, NF- $\kappa$ B and TLRs in rat intestine during CLP-induced sepsis. *Int Immunopharmacol* 2007;**7**:1076–1082.
  66. Sikand P, Premkumar L. Potentiation of glutamergic transmission by protein kinase C-mediated sensitization of TRPV1 at the first sensory synapse. *J Physiol* 2007;**581**:631–647.
  67. McNamee TA, Ma Y, Chen Y, et al. A peripheral neuroimmune link: glutamate agonists upregulate NMDA NR1 receptor mRNA and protein, vitmentin, TNF- $\alpha$ , and RANTES in cultured human synoviocytes. *Am J Physiol Regul Integr Comp Physiol* 2010;**298**:R584–R598.
  68. Zhang LP, Chen Y, Clark BP, et al. The role of type 1 metabotropic glutamate receptors in the generation of dorsal root reflexes induced by arthritis or the spinal cord infusion of 4-aminopyridine in the anesthetized rat. *J Pain* 2000;**1**:151–161.
  69. Chang Y, Lee JJ, Hsiao G, et al. Inhibitory effects of ketamine on lipopolysaccharide-induced microglial activation. *Mediators Inflamm* 2009;**2009**:705379. Epub.
  70. Manjunath S, Sakhare PM. Adenosine and adenosine receptors: newer therapeutic perspective. *Indian J Pharmacol* 2009;**41**:97–105.
  71. Mc Callion K, Harkin DW, Gardiner KR. Role of adenosine in immunomodulation: review of the literature. *Crit Care Med* 2004;**32**:273–277.
  72. Mazar J, Rogachev B, Shaked G, et al. Involvement of adenosine in the anti-inflammatory action of ketamine. *Anesthesiology* 2005;**102**:1174–1181.
  73. Welters ID, Hafer G, Menzebach A, et al. Ketamine inhibits transcription factors activator protein 1 and nuclear factor- $\kappa$ B, interleukin-8 production, as well as CD11b and CD16 expression: studies in human leukocytes and leukocytic cell lines. *Anesth Analg* 2010;**110**:934–941.
  74. Hill GE, Anderson JL, Lyden ER. Ketamine inhibits the proinflammatory cytokine-induced reduction of cardiac intracellular Adenosine accumulation. *Anesth Analg* 1998;**87**:1015–1019.
  75. Cadieux JS, Leclerc P, St-Onge M, et al. Potentiation of neutrophil cyclooxygenase-2 by adenosine: an early inflammation signal. *J Cell Sci* 2001;**118**:1437–1447.
  76. Pouliot M, Fiset ME, Massé M, Naccache P, Borgeat P. Adenosine up-regulates cyclooxygenase-2 in human granulocytes: impact on the balance of eicosanoid generation. *J Immunol* 2002;**169**:5279–5286.
  77. Chiang N, Schwab JM, Fredman G, Kasuga K, Gelman S, Serhan CN. Anesthetics impact the resolution of inflammation. *PLoS ONE* 2008;**3**:e1879.
  78. Li Y, Li BWan X, et al. NMDA receptor activation stimulates transcription-independent wnt5a protein synthesis via the MAPK signaling pathway. *Mol Brain* 2012;**5**:1. <http://www.molecularbrain.com/content/5/1/1>.
  79. Ghosh S, Hayden M. New regulators of NF- $\kappa$ B in inflammation. *Nat Rev Immunol* 2008;**8**:837–848.
  80. Sulibruk JW, Ward JL, Helmer KS, Adams SD, Zuckerbraun BS, Mercer DW. Ketamine-induced hepatoprotection: the role of heme oxygenase-1. *Am J Physiol Gastrointest Liver Physiol* 2009;**296**:G1360–G1369.
  81. Gao M, Qian Y, Ji L, Feng G, Sun J. Effect of N-methyl-D-aspartate receptor antagonist on T helper cell differentiation induced by phorbol-myristate-acetate and ionomycin. *Cytokines* 2011;**56**:458–465.
  82. Gao M, Sun J, Jin W, Qian Y. Morphine, but not ketamine, decreases the ratio of Th1/Th2 in CD4-positive cells through T-bet and GATA3. *Inflammation* 2012;**35**:1069–1077.
  83. Van Berkel BNM, Oranje B, van Ree JM, Verbaten MN, Kahn RS. The effect of low dose ketamine on sensory gating, neuroendocrine secretion and behavior in healthy human subjects. *Psychopharmacology* 1998;**137**:271–288.
  84. Hergovich N, Singer E, Agneter E, et al. Comparison of the effects of ketamine and memantine on prolactin and cortisol release in men: a randomized, double-blind placebo-controlled trial. *Neuropsychopharmacology* 2001;**24**:590–593.
  85. Damianopoulos EN, Carey RJ. Evidence for NMDA receptor mediation of cocaine induced corticosterone release and cocaine conditioned stimulant effect. *Behav Brain Res* 1995;**68**:219–228.
  86. Rofael HZ, Turkal RM, Abdel-Rahman MS. Immunomodulation by cocaine and ketamine in postnatal rats. *Toxicology* 2003;**188**:101–104.
  87. Roytblat L, Talmor D, Rachinsky M, et al. Ketamine attenuates the interleukin-6 response after cardiopulmonary bypass. *Anesth Analg* 1998;**87**:266–271.
  88. Bartoc C, Frumento R, Jalbout M, Bennett-Guerrero E, Du E, Nishanian E. A randomised, double-blind, placebo-controlled study assessing the anti-inflammatory effects of ketamine in cardiac surgical patient. *J Cardiothorac Vasc Anesth* 2006;**20**:217–222.
  89. Zeyneloglu P, Donmez A, Bilezikci B, Mercan S. Effects of ketamine on serum and tracheobronchial aspirate interleukin-6 levels in infants undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 2005;**19**:329–333.
  90. Yang Z, Chen ZQ, Jiang XQ. Effects of subanesthetic dose of ketamine on perioperative serum cytokines in orthotopic liver transplantation. *Nan Fang Yi Ke Da Xue Xue Bao* 2006;**26**:802–804.
  91. Dale O, Somogyi A, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. *Anesth Analg* 2012;**115**:934–943.
  92. Inaba H, Kochi A, Yorozu S. Suppression by methylprednisolone of augmented plasma endotoxin-like activity and IL-6 during cardiopulmonary bypass. *Br J Anaesth* 1994;**72**:348–350.
  93. Cremer J, Martin M, Redl H, et al. Systemic inflammatory response syndrome after cardiac operations. *Ann Thorac Surg* 1996;**61**:1714–1720.
  94. Hennein H, Ebba H, Rodriguez JL, et al. Relationship of the proinflammatory cytokines to myocardial ischemia and dysfunction after uncomplicated coronary revascularization. *J Thorac Cardiovasc Surg* 1994;**108**:626–635.

95. Oka Y, Murata A, Nishijima J, et al. Circulating IL-6 as a useful marker for predicting postoperative complications. *Cytokine* 1992;**4**:298–304.
96. Suzuki M, Haraguiti S, Sugimoto K, et al. Low-dose ketamine potentiates epidural analgesia after thoracotomy. *Anesthesiology* 2006;**105**:111–119.
97. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* 1997;**41**:1124–1132.
98. Remerand F, Le Tendre Ch, Baud A, et al. The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study. *Anesth Analg* 2009;**109**:1963–1967.
99. Celerier E, Rivat C, Jun Y, et al. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. *Anesthesiology* 2000;**92**:465–472.
100. Hutchinson MR, Bland ST, Johnson KW, et al. Opioid-induced glial activation; mechanisms of activation and implications for opioid analgesia, dependence and reward. *ScientificWorldJournal* 2007;**7**:98–111.
101. Hutchinson MR, Zhang Y, Shridhar M, et al. Evidence that opioids may have toll like receptor 4 and MD-2 effects. *Brain Behav Immun* 2010;**24**:83–95.
102. Hudetz JA, Iqbal S, Gandhi S, et al. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. *Acta Anaesth Scand* 2009;**53**:864–872.
103. Hu Z, Ou Y, Duan K, Jiang X. Inflammation: a bridge between cognitive dysfunction and Alzheimer's disease. *Med Hypotheses* 2010;**74**:722–724.
104. Ramlawi B, Rudolph JL, Mieno S, et al. C-reactive protein and inflammatory response associated to neurocognitive decline following cardiac surgery. *Surgery* 2006;**140**:221–226.
105. Wang Y, He H, Zhu W, Duan K, et al. The role of the TLR4 signaling pathway in cognitive deficits following surgery in aged rats. *Mol Med Rep* 2013;**7**:1137–1142.