Midazolam Impairs Immune Functions

It's Time to Take Care of Dendritic Cells

IN the report by Ohta *et al.*,[1] the authors demonstrate that midazolam inhibits the antigen-presenting functions of dendritic cells (DC) and interferes with DC-induced T-cell activation.

The innate immune system recognizes pathogens using so-called pattern-recognition receptors, which largely are expressed on antigen-presenting cells and especially on DCs. This innate immune response is immediate and has two major functions. The first function is to promote phagocytosis, thereby limiting pathogen dissemination. The second function is to allow induction of the adaptive immune response mediated by lymphocytes. This latter step is crucial to generating a long-lasting immune response. The process depends mainly on pattern-recognition receptors that mediate DC maturation and are required to induce the primary T-cell response.

After phagocytosis, proteins derived from the microorganisms are processed in specialized intracellular compartments to generate antigenic peptides, which are then loaded on major histocompatibility complex class II molecules (*e.g.*, human leukocyte antigen–DR [HLA-DR]) and present on the surface of DCs. These major histocompatibility complex–peptide complexes are recognized by T-cell receptors of the CD4+ T lymphocyte, which are central for organizing the adaptive immune response (fig. 1).

This process is critical to anesthesiology and critical care medicine because decreased HLA-DR expression on monocytes, which can differentiate into DC *in vivo*, is the only marker of immunity that consistently correlates with infection and clinical outcomes.[2] Indeed, major surgery, trauma, and severe sepsis may lead to decreased HLA-DR monocyte expression, a marker of decreased capacity for antigen presentation.[3] This decreased expression correlates with an increased incidence of nosocomial infection.[2,4] Among patients scheduled for major surgery, HLA-DR monocyte expression is significantly lower in nonsurvivors and among patients with postoperative septic complications.[5]

In addition, improved patient outcomes were recently demonstrated when granulocyte macrophage colony stimulating factor treatment was given to septic patients who had low HLA-DR expression on antigen-presenting cells.[6] Monitoring monocyte HLA-DR expression could be important to improving clinical course among patients with sepsis.[6]

However, recognition of complexes associated with peptide–major histocompatibility complex II is not sufficient to activate T cells, which require at least two signals before activation.[7] Although the first preactivation signal is the HLA-peptide complex, the second signal is provided by the presence of costimulatory molecules, such as CD80 and CD86. It is only when the same antigen-presenting cell expresses both signals that the T cell can be activated.[7]

DCs play a unique role in orchestrating the immune response for two reasons. First, DCs are the most potent antigen-presenting cells in the immune system. Second, DCs have the unique ability to activate naive T cells.[8] DCs are, therefore, essential for the initiation of any adaptive immune response and, therefore, are unique candidates for immunointervention.

Immature DCs, located in peripheral tissue—and especially in epithelia—specialize in antigen capture and pattern-recognition receptors that, in turn, trigger migration to draining lymph nodes where they become potent antigen-presenting cells. Yet, the picture is actually more complex than that because several DC subsets have been described both in peripheral tissues and lymphoid organs. Among them, plasmacytoid and conventional DCs are major players in host defense.[7,9]

Plasmacytoid DCs are found in all lymphoid organs[9] and are thought to be important in antiviral response because they are a major source of type I interferon on viral stimulation. In mice, conventional DCs are critically involved in bacterial control. CD8+ conventional DCs produce considerable amounts of interleukin 12, induce a strong T helper 1 cell response, and efficiently cross-present antigens to CD8+ T cells. CD8− conventional DCs were shown to produce interleukin 10 and drive T helper 2 responses. However, DCs exhibit a high-functional plasticity that depends on the nature of the initial pattern-recognition–receptor stimulation and microenvironment. The innate immune response relies on close collaboration among these three DC subsets.[9]

Ohta *et al.*[1] increase our understanding of midazolam-induced DC alterations. Indeed, in their experiments,[1] severe DC alterations were observed (*i.e.*, decreases in HLA-DR, CD80 and CD86 expression, and interleukin 12 p40 production). It is noteworthy that these phenotypic alterations were accompanied by functional defects as assessed by the inability of midazolam-treated DC to induce naive T-cell activation. It is at this point that a major limitation of this experimental study should be noted, however. From a pharmacologic point of view, the lowest midazolam concentra-

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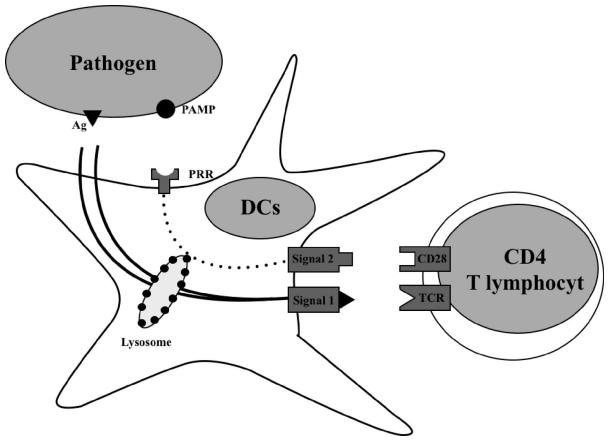

Fig. 1. Two pathogenic components are essential to inducing adequate immune response, namely antigens (Ag) and pathogen-associated molecular patterns (PAMPs). After phagocytosis, antigens are processed in the lysosome and form a complex with human leukocyte antigen–DR (HLA-DR) on the surface of dendritic cells (DCs). This complex is recognized by T-cell receptors (TCR). Stimulation of PAMP-recognition receptors activates DCs and induces membrane expression of the costimulatory molecules CD80 and CD86. Activation of CD4+ T lymphocytes requires the membrane expression of two distinct signals: (1) HLA-peptide complexes, and (2) costimulatory CD80 and CD86. It is only when the same antigen-presenting cell expresses both signals that the T cell is activated.

tion used, 5 μM, showed an effect in the dose-response curve and should, therefore, be used for subsequent experiments. Although the majority of experiments conducted by Ohta *et al.*[1] were performed with 15 μM midazolam, their results remain informative because that concentration has clinical relevance.

The midazolam-induced alterations observed in DCs are important from a clinical point of view because (1) midazolam is widely used for sedation in intensive care units, (2) midazolam induces a decrease of HLA-DR expression on DCs—a major marker of nosocomial infection in intensive care patients and after major surgery, and (3) the financial cost of one case of nosocomial pneumonia (*i.e.*, the most common cause of nosocomial infection in intensive care units) is approximately $10,000 (15,000–20,000€) per episode.

In conclusion, we strongly believe that future research for designing new drugs for use in anesthesiology and critical care should aim at testing their effects on immunity, particularly on DCs.

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