Alpha-2B Adrenergic Receptor Mediated Hemodynamic Profile of Etomidate

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Etomidate has been used since 1972 as an inductor and in maintaining anesthesia. There are multiple mechanisms that account for the biologic effects of etomidate. One of the most prominent features of this drug is that it provides anesthesia without gross changes in hemodynamic parameters. This feature allows using etomidate in patients with considerable cardiopulmonary compromise avoiding the characteristic hypotension produced by other anesthetics. The mechanism that provides the basis for its cardiovascular stability is the capacity to bind and stimulate peripheral alpha-2B adrenergic receptors with a subsequent vasoconstriction. Alterations in the function or number of these receptors may account for abnormal responses during etomidate induction. [*P R Health Sci J 2010;2:91-95*]

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Etomidate is a carboxylated imidazole-containing anesthetic compound (R-1-ethyl-1-[a-methylbenzyl] imidazole-5-carboxylate) that is structurally unrelated to any other IV anesthetic (1). Etomidate, a potent, short-acting hypnotic, was introduced into clinical anesthesia in 1973 (2). Etomidate has an onset of action of 3-5min, with a peak effect of 1 minute and duration of 3-5 minutes (3). The high clearance rate of etomidate (18 to 25 mL/kg/min) is a result of extensive ester hydrolysis in the liver (1).

When used for tracheal intubation, etomidate does not effectively blunt the sympathetic response to laryngoscopy, unless combined with a potent opioid analgesic (1). In addition, a study found no clinically significant hemodynamic changes after etomidate administration in children supporting the clinical impression that etomidate is also safe in this population (4), although there is inadequate data to make dosage recommendations for induction of anesthesia in pediatric patients below the age of ten years; therefore, such use is not recommended (5).

Etomidate is also known for its neuroprotective properties. Etomidate has been used successfully for both induction and maintenance of anesthesia for neurosurgery (1). Nevertheless, due to its well-known inhibitory effect on adrenocortical synthetic function (6), its clinical usefulness for long-term treatment of elevated intracerebral pressure (ICP) is limited. The inhibition on corticosteroids synthesis is a widely recognized effect that may persist for 5 to 8 hours after a single dose of induction (1). In addition, the Institute for Safe Medications Practices has classified etomidate as a high risk medication and has heightened the risk of causing significant patient harm when used in error.

Etomidate is widely used because it causes minimal cardiorespiratory depression even in the presence of cardiovascular and pulmonary disease (7). The drug does not induce histamine release and can be safely used in patients with reactive airway disease. Consequently, etomidate is considered to be the induction agent of choice for poor-risk patients with cardiorespiratory disease, as well as in those situations in which preservation of a normal blood pressure is crucial (e.g., cerebrovascular disease) (1).

Regarding these properties, it is important to emphasize that, in spite of its side effect profile, etomidate still remains a valuable induction drug for specific indications (in patients with severe cardiovascular and cerebrovascular disease) (1). Little is known about the mechanism responsible of its cardiovascular effects. Our review will focus in describing how the interaction with the α-2B adrenergic receptors may account for its properties and how this interaction may produce a predictably different cardiovascular profile in specific clinical situations.

Mechanisms of Etomidate

In humans, the anesthetic effect of etomidate is thought to be mediated primarily through an action on gamma-aminobutyric acid type A (GABAA) receptors (8-9) Effects on different GABAa

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receptor subtypes are related to specific actions. Data available for etomidate point to ß-3-containing GABAA receptors mediating immobility and respiratory depression, in part hypnosis and, to a minor degree, hypothermia, while ß-2-containing GABAA receptors mediate, for the most part, hypothermia, and in a lesser degree hypnosis and sedation (10).

Etomidate also has a known inhibitory effect on adrenocortical synthetic function (11), which is mediated by inhibition of the activity of 11-β-hydroxylase, an enzyme necessary for the synthesis of cortisol, aldosterone, 17-hydroxyprogesterone, and corticosterone (12). A single induction dose of etomidate produces an adrenal suppression that persists for 5 to 8 hours (1). It is speculated that this effect is responsible for the increased mortality in critically ill patients sedated with an etomidate infusion (1). Another study showed that a single-dose etomidate for RSI in severely injured trauma patients is associated with increased Adult Respiratory Distress Syndrome (ARDS) and multiple organ dysfunction syndrome, in part, because of the effect of etomidate on the inflammatory response (13). Etomidate has been also shown to inhibit platelet function, resulting in prolongation of the bleeding time (14). Most studies agree that the sedative properties of etomidate are mediated by alpha-2 and GABAa receptors (8-9), but when we turn our look to evaluate the mechanism responsible of the hemodynamic stability associated with etomidate, the information is not as conclusive.

A study showed that etomidate increases the responsiveness to norepinephrine in an endothelium-dependent way, which is partially independent of the action of nitric oxide (NO), endothelium-derived hyperpolarizing factor (EDHF), cyclooxygenase products, lipooxygenase products, angiotension-II and Endothelin (15). It was also established that endothelium denuded arteries have a decreased contractile response to norepinephrine, which is mediated by a low intracellular calcium and a decreased calcium sensitivity of the myofilaments in the vascular smooth muscle cells (15). Regarding a calcium-related mechanism, etomidate inhibited angiotensin (AT) II-induced $Ca2^{++}$ mobilization in cultured rat aortic smooth muscle cells (15).

On the other hand, etomidate (5–300 uM) inhibited the vasodilator response to endothelium-derived nitric oxide (EDNO) or endothelium-derived hyperpolarizing factor (EDHF) in isolated human renal arteries (15). EDHF is thought to be a cytochrome P450-derived arachidonic acid metabolite that hyperpolarizes vascular smooth muscle cells by opening Ca^{2++}-activated Potassium sup + channels (K sup $+_{Ca}$ channels). Etomidate inhibits the EDHF-mediated relaxant response to acetylcholine in the human renal artery, an effect that appears to be attributable to the cytochrome P450-inhibiting properties of this anesthetic (16).

Other studies have shown a critical role for potassium-ATP (KATP) channels. In vascular smooth muscles, opening of KATP channels leads to membrane hyperpolarization, resulting in muscle relaxation and vasodilation (17). Etomidate (1–100 uM) inhibited the vasodilator response to ATP-sensitive K (KATP) channel openers in isolated canine pulmonary arteries and rat aortas and inhibited the activities of vascular KATP channels at clinical concentrations (18).

Interactions of etomidate with second messenger systems such as the NO metabolism have been shown (19) and it has been found that alpha 2B-adrenoceptor subtype is involved in mediation of the antinociceptive action of nitrous oxide (20-21).

A new perspective focuses on the structural similarity between carboxylated imidazole etomidate and specific alpha 2-adrenoceptor agonists that belong to the class of imidazole compounds, such as clonidine and dexmedetomidine (22-23).

The following figure shows the structure of Etomidate and Dexmedetomidine (24):

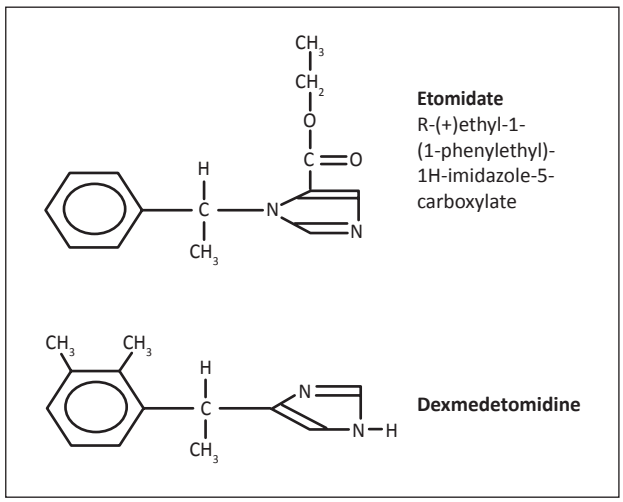

Figure 1. Alpha-2 receptors and their roles

These receptors are located primarily on presynaptic nerve endings and on other cells, such as the ß cell of the pancreas, and control adrenergic neuromediator and insulin output, respectively. When a sympathetic adrenergic nerve is stimulated, the released norepinephrine traverses the synaptic cleft and interacts with the (alpha-1 receptor). The stimulation of the alpha-2 receptor causes feedback inhibition of the ongoing release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action decreases further output from the adrenergic neuron and serves as a local modulating mechanism for reducing sympathetic neuromediator output when there is high sympathetic activity. In contrast to alpha-1 receptors, the effects of binding at alpha-2 receptors are mediated by inhibition of adenylyl cyclase and a fall in the levels of intracellular cAMP (25). Three subtypes of alpha-2-adrenoceptors, termed alpha-2A, alpha-2B, and alpha-2C, have been cloned from several species including mice and humans

(26-27). Alpha 2-receptor subtypes are encoded by distinct genes which are localized on separate chromosomes (24) and have been characterized pharmacologically and by cloning their cDNAs (28).

Alpha 2A-adrenoceptor subtype has been reported to be the predominant subtype involved in the antinociceptive, sedative, hypotensive, hypothermic, and behavioral actions of alpha-2 adrenoceptor agonists (29-32). Antinociceptive response to an exogenous alpha-2 agonist is mediated by an alpha-2A adrenoceptor (20). A study found that β2-adrenoceptors sensitizes α2A-adrenoceptors to desensitization after chronic epinephrine treatment (33). In the central nervous system, the alpha-2A subtype is the most prevalent and ubiquitous of the three, whereas alpha-2B is only present in a few discrete sites, principally the thalamic nuclei, and then in very small amounts (20).

Stimulation of alpha 2B-adrenoceptors in vascular smooth muscle leads to vasoconstriction, which causes the initial hypertension after administration of alpha 2-adrenoceptor agonists (22). In addition, the alpha-2B-adrenoceptor subtype is involved in mediation of the antinociceptive action of nitrous oxide (20-21). A polymorphism of the alpha-2B AR gene with three glutamic acids deleted from a glutamic acid repeat element (GluX12, amino acids 297–309) in the putative third intracellular loop of the receptor protein was identified (34- 35), and obese patients with the mutation in both alleles were found to have a lower basal metabolic rate (BMR) (34). Heart rate variability is also influenced by these receptors. A study showed that, carriers of Short/Short (both alleles with the three glutamic acids deleted, see above) had significantly greater low frequency and very low frequency than Long/Long carriers, as well as a higher sympathetic nervous system index (36). Another study found that non-diabetic carriers of a polymorphism of the alpha-2B receptor (three glutamic acids deleted at position 297-299) have increased predisposition to Arterial Hypertension. The mechanism involved appears to be impaired agonist induced desensitization (37).

Alpha 2C-receptor has been shown to modulate dopaminergic neurotransmission, various behavioral responses, and to induce hypothermia (38-39). In addition, this subtype contributes to spinal antinociception of the imidazoline moxonidine in mice (40).

Etomidate and alpha-2B receptors

Several studies have provided evidence regarding the hemodynamic stability associated with etomidate and its capacity to stimulate alpha-2B receptors based on its structural similarity with alpha-2 agonists. The current information is that mice and animals lacking functional alpha-2A receptors show no difference with controls regarding their capacity to be sedated/hypnotized, suggesting that alpha-2A receptors appear to be unnecessary for etomidate to produce sedation/hypnosis. In addition, it is known that etomidate has higher affinity for alpha-2B and alpha-2C receptors than alpha-2A receptors (24). Disruption of the alpha-2C adrenoceptor subtype does not lead to hemodynamic effects (22). However, alpha-2C-receptors operate together with alpha-2A receptors as presynaptic inhibitory regulators of sympathetic norepinephrine release (41). In a study using wild-type mice and mice lacking alpha-2A or alpha-2B receptors, a rapid intravenous injection of dexmedetomidine resulted in a transient hypertension in wild-type mice that was followed by a long-lasting hypotension. Deletion of the alpha-2A receptor disrupted the hypotensive response, whereas the initial hypertension was absent in alpha-2B-deficient animals (22).

Administration of dexmedetomidine in mice lacking both alpha-2A and alpha-2B receptors, failed to produce the initial hypertension, which can be attributed to the alpha-2B adrenoceptor subtype (33) and the central hypotensive effect related to the alpha-2A adrenoceptor subtype (30). These findings are consistent with the observation that activation of presynaptic sympathetic alpha- 2C receptors can decrease norepinephrine release (41).

Other authors have also described this biphasic response to the intravenous response of an alpha-2 agonist (22). They described an initial phase in which mean arterial pressure rises transiently as arterial alpha-2 AR constrict vascular smooth muscle (42) and that, after this initial hypertensive response, mean arterial pressure drops below baseline because alpha-2 AR in the ventrolateral medulla oblongata attenuate symphathetic and accentuate parasymptathetic outflow (43). Considering that central hypotensive response is not mediated by alpha 2B or C receptors, they conclude that alpha-2A subtype is important in the control of the central sympathetic outflow (22).

Although this initial view seems to support the concept that the early hypertensive response is mediated by alpha-2B receptors, subsequent hypotensive response is mediated by alpha-2A receptors and no important role for alpha-2C is seen in mediating hemodynamic changes. It is important to take into consideration that alpha-2B subtype receptors are found primarily in the brain, liver, lung and kidney, with the highest amounts in the kidney. The fact that this response is observed rapidly, arises doubts concerning the role of alpha-2B receptors in the kidney, although evidence of a relation with the hypertensive response observed after salt loading has been described (44).

Considering that evidence supporting that hemodynamic changes observed during the induction with etomidate are grossly due to the agonist effect on alpha-2 receptors, we inquired about the effects that could produce abnormal functioning or availability of alpha-2 receptors in the hemodynamic response to etomidate.

Focusing on the initial hypertensive response mediated primarily by peripheral alpha-2B receptors, we found some information regarding abnormal states of functioning of these receptors. It is known that all these receptors (alpha-2)

couple to the inhibitory heterotrimeric GTP-binding protein (Gi) and inhibit adenyl cyclase (22). A polymorphism of alpha-2B adrenergioreceptor consisting of a deletion of three glutamic acids (residues 301–303) from a glutamic acid repeat element in the third intracellular loop has been associated to a small decrease in the coupling efficiency, resulting in reduced inhibition of adenylyl cyclase (45), with a reduced basal metabolic rate in obese subjects, with an increase in body weight among nondiabetic subjects, and modulation of autonomic nervous function in nondiabetic men (45). Normal alpha-2B receptors undergo term agonist promoted desensitization which involves phosphorylation of the receptor that ultimately produces uncoupling of the receptor with its Gi effector protein. Initial phosphorylation is mediated by a G protein-coupled receptor kinase (GRK) member of the serine/threonine kinase family. This enzyme requires the presence of acidic residues (mainly Glutamic Acid residues) in the third intracellular loop of the receptor and the deletion of these residues (polymorphic variant of the alpha-2B receptor described above) produce a deficiency in the functioning of the phosphorylating enzyme and a defective phosphorylation of the receptor and, consequently, decreased desensitization. Desensitization may also limit the therapeutic effectiveness of administered agonists (44). Different allele frequencies for this polymorphism have been established between racial groups, being more common in Caucasians (allele frequency 0.31) than in African Americans (allele frequency 0.12) (45). This polymorphism has also been associated to higher predisposition to essential arterial hypertension in Swedes (37), in which the mechanism presumably is impaired agonist desensitization. Little is available about etomidate (as an alpha-2 agonist) producing marked hypertensive effects and/or a more pronounced response in carriers of this polymorphism. The association of the α2B-AR genotype with either hypertension and coronary events or BMR and obesity needs to be tested in other well-designed genetic studies (46).

Resumen

Etomidato ha sido usado desde 1972 como un agente inductor y para mantener anestesia. Existen múltiples mecanismos que dan cuenta de los efectos biológicos de Etomidato. Una de las características más sobresalientes de este fármaco es su capacidad de proveer anestesia sin producir cambios mayores en los parámetros hemodinámicos. Esta característica permite usar Etomidato en pacientes con considerable compromiso cardiopulmonar, evitando la característica hipotensión producida por otros anestésicos. Un mecanismo identificado como responsable de la estabilidad cardiovascular asociada es su capacidad de estimular receptores alpha-2B periféricos que tiene como consecuencia una vasoconstricción. Alteraciones en la función y número de estos receptores pueden dar cuenta de respuestas anormales durante la inducción con Etomidato.

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