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A review of neuroprotective mechanisms of dexmedetomidine

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Abstract: Dexmedetomidine (DEX) is a highly specific and effective α2-adrenergic receptor agonist. Due to its high protein binding rate, intravenous pumping can play a good role in sedation and hypnosis, analgesia, anti-anxiety, reducing inflammation, and so on, so it has been widely used in clinical anesthesia and basic research. In recent years, with the further study of dexmedetomidine, it has been found that it has a certain protective effect on nerve injury caused by various causes.

1. Introduction

In recent years, with the deepening of research, the advantages of dexmedetomidine in the protection of nerve injury caused by various reasons have been paid attention, such as preventing the occurrence of postoperative cognitive dysfunction, reducing the degree of hypoxia-reoxygenation brain injury and hypoxia-reoxygenation spinal cord injury, and reducing post-traumatic brain injury and hypoxic-ischemic injury. This article reviews the neuroprotective mechanism of dexmedetomidine in order to provide direction for further clinical treatment.

2. Mechanism of neuroprotective effect of dexmedetomidine

2.1 Acts on the α2A subtype receptor

2.1.1 Inhibition of excitatory amino acids

Glutamic acid is an excitatory amino acid normally expressed in human body and plays an important role in maintaining normal electrophysiological activities of cells. When the brain is traumatized, glutamic acid content can increase rapidly in a short time, causing toxic effects and aggravating cell damage. Several studies have demonstrated that DEX exerts a neuroprotective effect on α2-R by reducing its content in glutamate sources, presynaptic membranes, and synaptic cleta. Glutamine as its source increases glutamine metabolism in astrocytes[1]; Acts on presynaptic membrane Ca2+ channels to reduce release[2-3]; Act on astrocytes to remove excess glutamate from synaptic cleft[3]; PKC and PI3K activities were enhanced[4] to further increase the expression of

glutamate transporters and thus accelerate the clearance of glutamate in synaptic cleta. Through the above mechanism, DEX can effectively reduce the secondary damage of glutamic acid on nerve cells.

2.1.2 Inhibition of central and peripheral catecholamine release

When the body is in a state of stress, a large number of catecholamines (epinephrine, norepinephrine, etc.) are released into the blood. By combining with α2-R in the central and peripheral areas, on the one hand, it can lead to the reduction of blood supply in the corresponding parts, the enhancement of cell metabolism and aggravation of hypoxic injury of nerve cells. On the other hand, it can be used as a nerve cell sensitizer to excitatory glutamate, exacerbating the toxic effect of the latter in excess. DEX can activate the rectifying inward potassium channel, cause the outflow of intracellular K+, and block the inflow of extracellular Ca2+, so that the cell is in a hyperpolarized state, unable to release the transmitter. Other studies have shown that dexmedetomidine can promote the expression of anti-apoptotic proteins Mdm-2 and Bcl-2 and regulate the release of catecholamine, thus protecting nerve cells from neurotransmitter toxicity.

2.1.3 Anti-apoptotic expression and autophagy

Apoptosis, also known as programmed cell death, usually occurs in the late stage of injury and has a unique role in the normal development of tissues or organs. DEX may exhibit anti-apoptotic properties by regulating both pro-apoptotic proteins (such as Bax, BAD) and anti-apoptotic proteins (B-cell lymphoma/leukemia-2 (Bcl-2), BCL-XL) in cells. DEX also activated focal adhesion kinase (FAK), which further activated the anti-apoptotic AKT/ PI3K and ERK1/2 pathways. Increasing the concentration of MDM2 decreased the activity of p53 to reduce cell apoptosis, and increased the phosphorylation levels of p38 MAPK and ERK1/2 to counteract OGD-induced apoptosis. In conclusion, the upregulation of BCL2, pERK and Bcl-xl by the above mechanisms further prevents the release of CytC from mitochondria, and downregulates the pro-apoptotic proteins Bax and P53 for neuroprotective purposes [5].Cao Yan, Jiang Hongyan, Wang Yanxue et al.[6] used Western blot to detect the protein content in the cerebral cortex 10 minutes before traumatic brain injury (TBI) modeling and found that: Compared with the blank control group, the normal saline group, DEX group and SIRT1 inhibitor EX527 group, the latter two groups increased the expression of Bcl-2 protein and decreased the expression of Bax protein, and DEX group had the most significant effect. It is speculated that the mechanism is related to the SITR1 pathway, which plays an anti-apoptotic mechanism to protect nerve function. In addition, Caspase-3 is a key enzyme in the caspase family, which is cysteine aspartic protease. Zhao Qian and Yang Jian[7] also explained that DEX pretreatment could reduce the neurological side effects of propofol and other anesthetic drugs, and bolder speculated that the action pathway was related to the ERK1/2 pathway and BNDF pathway, which increased the expression of Bcl-2 and decreased the expression of Caspase-3.

Some scholars believe that autophagy is the first stage of cell apoptosis. Autophagy is a second-order programmed death in eukaryotic cells, which can be activated by various inductions (drugs, injuries, etc.).The degree and time of autophagy can produce different results. Moderate autophagy in the early stage can remove excessive reactive oxygen species and damage organelles, while excessive autophagy in the late stage will destroy the permeability of lysosomal membrane, and a large number of lytic proteases will enter the cytoplasm and damage the cell. Tang Ying, Li Xinmei, Wang Xue et al.[8] studied the specific effect of DEX on autophagy mechanism by establishing an OGD/R model of nerve cells. The results showed that the activity of nerve cells increased after DEX treatment, and the number of cell/mitochondrial autophagosomes increased, and the expression of autophagy-related proteins Bcl-2, P62 and TOM20 increased significantly.

The expressions of Beclin 1 and LC3II/LC3I proteins were significantly decreased. Therefore, the authors suggest that DEX exerts neuroprotective effects by inhibiting over-upregulated autophagy.

2.1.4 Increase the expression of growth factors

It has been verified that astrocytes not only provide metabolites, shuttle ions and water, but also scavengers ROS and reactive metals to protect neurons after cerebral ischemia. They also regulate inflammatory responses, are involved in cell debris clearance, and provide trophic factors to neurons. One of the highlights of Yan M, Dai H, Ding T, etal. [9] is that DEX can stimulate astrocytes to secrete glial cell line-derived neurotrophic factor (GDNF). It is the first time to demonstrate that this protective effect can be directly exerted on a2-AR in a time - and dose-dependent manner, which can be blocked by α2-R antagonist yohimbine and α2-adrenoceptor siRNA, but not by α1-R antagonist prasozin. Further studies confirmed that this process was PKCa and CREB dependent.

2.2 Cell effects mediated by non-α2 adrenergic receptors

2.2.1 Regulate extracellular signal transduction molecules and promote the opening of ATP-sensitive K+ (KATP) channels

ERK1/2 (Extracellular signal-regulated kinase), Chinese name mitogen activated protein kinase 1/2, is a member of the mitogen activated protein kinase signaling family, regulates cell proliferation and differentiation, and is associated with neuroprotection. ERK is a key enzyme in cell metabolism activated by many different types of tissue damage and is thought to have a "survival" function. Wang Y, Han R and Zuo Z showed[10] that activation of ERK was an important factor in DEX's protection of traumatic nerve tissue, and the same conclusion could be reached even after delayed administration of the drug after trauma. In addition, another scholar[11] found that DEX had a dose-dependent protective effect on hippohippocampus cells, and the dose-effect curve was U-shaped, with the strongest effect when the concentration was 1μM.Therefore, the authors conclude that the protective effect is at least partially mediated by ERK, as they are offset by the co-administration of PD98059.

Present results suggest[12] that DEX inhibits IK+(DR) (delayed rectifier potassium channel) in a concentration - and state-dependent manner in differentiated NG108-15 neurons. DEX also blocked the peak amplitude of INa+ (Na+ current), while it had little effect on ICa2+-L (L-type Ca2+ current), suggesting that DEX might exert its inhibitory effect on IK+(DR) by interacting with the imidazoline binding site. It has been mentioned in literature[13] that this mechanism can enhance phosphorylation of ERK1/2 and DEX to play a neuroprotective role.

2.2.2 Inhibit inflammation

Sepsis is a syndrome of imbalance between inflammatory response and anti-inflammatory response in multiple organs of the body caused by a variety of pathogenic microorganisms (such as bacteria, viruses, fungi, etc.) infection from various parts of the body. It can cause widespread systemic inflammation, neuroinflammation, blood-brain barrier leakage and impaired neurocognitive function. The brain is a manifestation of systemic inflammatory reactions, which can lead to sepsis associated encephalopathy (SAE).The main clinical manifestations are distraction, trance, irritable mood, lethargy and coma. Mei B, Li J, Zuo Z.[14] found that systemic administration of DEX attenuated these pyotoxic effects and speculated that the neuroprotective effect of DEX may be mediated by α-2A adrenergic receptors in astrocytes rather than microglia (rather than imidazoline receptors).Luo Zi and Hu Xiaoling[15] also outlined that DEX may play an

anti-inflammatory role by inhibiting the cascade expression of inflammatory factors after activation of central and peripheral macrophages, TLR4/NF-κB pathway and activating cholinergic anti-inflammatory pathway.

2.2.3 Inhibit oxidative stress

Oxidative stress injury plays an important role in the evolution of brain injury caused by various causes. ROS represented by superoxide anion can maintain the REDOX system of cells in a steady state under physiological conditions. When the body's ability to scavengers free radicals is reduced or the antioxidant substances (superoxide dismutase, SOD, and glutathione peroxidase, GSH-Px) are deficient, the body is in a state of oxidative stress. The peroxidation of proteins, lipids and nucleic acids in the neuronal cell membrane destroys the integrity of the cell membrane, which can lead to a sharp decrease in cell number due to necrosis. Akpınar H, Nazıroğlu M, Oveişs, etal[16] found that DEX reduced cerebral ischemia-induced oxidative stress, cell death, and intracellular Ca2+ signaling by inhibiting TRPM2 and TRPV1 in the hippocampus and DRG of rats. These findings could explain the cerebral ischemia-induced HIPPO and DRG injury. Therefore, DEX is speculated to have a neuroprotective effect by acting on the above processes. This study prospectively suggests that the inhibitory effect of DEX on ischemia-induced activation of TRPM2 and TRPV1 may be a potential pharmacological target for brain injury. Sifringer M, von Haefen C, Krain M, etal.[17] demonstrated for the first time that DEX reduced IL-β gene overexpression induced by hyperoxy, and a single dose could decrease apoptosis rate, increase GSH/GSSG ratio, and decrease lipid peroxidation. Reduce or eliminate the adverse effects of high oxygen environment and play a neuroprotective role.

2.2.4 Acting on imidazoline receptors

DEX contains imidazoline structure and has a certain affinity for imidazoline receptors. There are three known subtypes of imidazoline receptors, I1, I2, and non-I1/2 (I3).Studies have shown that the neuroprotective effect of DEXM is mainly regulated by I2 imidazoline receptors in the frontal cortex, and has little relationship with I1 or I3 imidazoline receptors. Zhang F, Ding T, Yu L, etal. [18] confirmed that dexmedetomidine activates I2-PI3K/AKT pathway and up-regulates HIF-1 (hypoxia-inducing factor), VEGF (vascular endothelial growth factor) and RTP801 (REDD1, The expression of developmental and DNA damage response regulatory gene 1) protects rat C6 cells from OGD-induced damage.

2.2.5 Effects on cerebral blood flow, cerebral metabolism and intracranial pressure

Some scholars have measured the velocity of middle cerebral artery and jugular venous oxygen saturation (SvO2), and found that the ratio of CBF (cerebral blood flow) /CMR (cerebral metabolic rate) in humans treated with DEX sedation did not decrease. Other studies using sagittal outflow techniques in dogs anesthetized with isoflurane or flurane have reported no effect of DEX on CMR. However, these studies reflect global or hemisphereal cerebral metabolic status rather than regional O2 supply/consumption balance. Chi OZ, Hunter C, Liu X, etal[19] made the following conclusions through research: in normal blood volume, DEX can reduce rCBF (regional cerebral blood flow) and O2 consumption in proportion. Hemorrhage reduced rCBF more than O2 consumption. DEX may help to provide optimal rCBF and O2 consumption balance during severe hemorrhagic hypotension by reducing rCVR (regional cerebral vascular resistance) and brain metabolism, helping to establish optimal oxygen supply and demand balance during hemorrhage. Thus, the features of DEX that prevent further reductions in rCBF and O2 consumption during hemorrhage may contribute to the neuroprotective effects reported by DEX. Wang Jiaoyan, Wang Jiangang,

Zhang Wenjie et al.[20] found that DEX could not only provide clinical sedation, but also reduce cerebral oxygen metabolism and significantly reduce the diameter of middle cerebral artery, effectively maintaining the balance between cerebral oxygen supply and demand.

2.3 Influence of gene expression

DEX can play a protective role by mediating gene expression in nerve cells[21-22].microRNAs (miRNAs) are endogenous, non-coding single-stranded Rnas that can pair with the mRNA of protein-coding genes to direct their repression and further mediate important gene regulatory events, such as apoptosis and proliferation. In previous neuroprotective studies, few scholars have described the effect of Dex through antioxidant damage. In addition, although miRNAs have been reported to play a role in neurodegenerative diseases, few studies have mentioned the relationship between miR-199a and hypoxia. Wu L, Xi Y, Kong Q[23] found the protective mechanism of DEX against oxidative damage induced by H2O2 in PC12 cells (adrenal pheochromocytoma, a sympathetic nervous system tumor in Rattus norgicus), DEX could significantly down-regulate the expression of miR-199a induced by H2O2, further up-regulate the increased content of HIF-1α on the basis of oxidative damage, and activate PI3K/AKT/mTOR and Wnt/β-catenin pathways. The experiments of Zhu Y, Zhao H, Zhang W, etal[24] supported the above conclusion, and also showed that DEX inhibited the expression of miR-199a after CIR (cerebral ischemia-reperfusion) and improved CIR-induced nerve cell damage, which was consistent with the above results.

2.4 Modulating synaptic plasticity and long-term hippocampal enhancement (LTP) effect

Synaptic structure is the hub of functional connections between various neurons or neurons and other types of cells in the reflex arc, which can be divided into electrical synapses and chemical synapses, with the latter being the majority. In physiology, synaptic plasticity mainly refers to the change of synaptic efficiency, which can be divided into long-term change and short-term change according to the maintenance time of the change. The former mainly includes long-term enhancement (LTP) and long-term suppression (LTD). Synaptic plasticity is widespread in the nervous system and is closely related to learning and memory. Compared with previous brain slice experiments, multiple studies have found that a single dose of DEX mediates synaptic plasticity in the hippocampal CA1 region through β receptors, which is more relevant to spatial learning. It is hypothesized that DEX inhibits LTP induced by θ stimulation (TBS) by activating α2-adrenergic receptors and imidazoline I2 receptors. The most plausible mechanism is that DEX activates the postsynaptic α2-adrenocepter and subsequently reduces the α2-adrenocepter induced late LTP-high frequency stimulation-triggered synthesis of new proteins and decreases the release of norepinephrine.

However, other studies have shown that DEX can enhance LTP, inhibit neuronal apoptosis, and play a protective role when it binds to α2 receptors in the presynaptic membrane to inhibit the release of glutamate in the cerebral cortex. Zhou L, Qin SJ, Gao X, etal[25] used the cerebral ischemia model of post-ischemic LTP (i-LTP) to analyze whether and how DEX could functionally prevent the pathological form of synaptic plasticity induced by ischemia in hippocampal CA1 neurons. The neuroprotective effect of DEX is mediated by decreasing the release of NE and glutamate at presynaptic level and promoting the hyperpolarization of the postsynaptic membrane, which further regulates the postsynaptic inhibition of NMDAR activation through the β receptor and the downstream cAMP/PKA pathway. The latest study by Zhang L, Zhang P, Wang G, etal[26] found that at the same synapse, homologous Ras and Rap proteins use different subcellular microdomains to produce a variety of specific signal responses in rat CA1 hippocampal neurons. For example, endogenous Ras first signals synaptic enhancement through the PI3K pathway in the

endoplasmic reticulum and the lipid raft ERK pathway, while Rap2 and Rap1, belonging to the Ras family of small gtpase, act on the lysosomal p38MAPK and JNK pathways to signal synaptic inhibition. These new findings support that Ras is involved in synaptic plasticity and that the above-mentioned proteins can separately regulate different forms of synaptic plasticity in the same synapse. The above studies indicate that DEX can regulate synaptic plasticity and play a neuroprotective role.

2.5 Reduce nerve damage caused by other narcotic drugs to brain tissue in development and adulthood

Individuals with underdeveloped brain tissue may experience structural and functional dysfunction of nerve cells after general anesthesia, leading to neurodegeneration. The protective effect of DEX on the developing nervous system is mainly reflected in the dose-dependent increase of neurotransmitters such as BNDF, inhibition of nerve cell apoptosis and autophagy, anti-hyperoxia oxidation, reduction of inflammatory response after ischemia-reperfusion, interference of gene expression, and reduction of cranial temperature (the mechanism remains to be studied)[错误!未找到引用源。]. In addition, DEX has also been used in clinical studies to protect the developing brain tissue. This has been mentioned in the previous mechanism. Some studies[28-29] have found that DEX can activate PI3K/Akt signaling pathway to reduce short-term and long-term neurological damage induced by propofol in young rats, proving that DEX is relatively reliable when used in the developmental period, and clinical experiments have demonstrated that Dex has a protective effect on postoperative cognitive function in adults.

2.6 Acts in glial cells

Glial cells, referred to as glial cells, together with neurons constitute the cells of the nervous system, the former being about 10-50 times the magnitude of the latter. Glial cells are widely distributed, including astrocytes, microglia and oligodendrocytes in the central nervous system. There are Schwann cells and satellite cells in the peripheral nervous system.

Astrocytes are the most numerous and versatile glial cells in CNS. Under physiological conditions, it uses perivascular feet and processes to build Bridges between capillaries and neurons to deliver nutrients to nerve cells and expel metabolites. However, once activated by pathological injury, it will rapidly respond to injury, resulting in hyperplasia and release of a variety of pro-inflammatory factors to play a negative role. DEX can reduce the expression of inflammatory cytokines in LPs-induced astrocytes, and this effect may be closely related to the JNK pathway [30].

Microglia are mononuclear macrophage systems that first respond to nerve injury and inflammation, and adapt to the external environment by adjusting their functions and cell phenotypes[31]. It has been confirmed that microglia polarize into two forms, M1-like phenotype and M2-like phenotype. Among them, the former is related to the induction of proinflammatory response, while the latter plays a role in neuroprotection [32].Some scholars have studied the anti-inflammatory effect of DEX on BV2 microglia treated with lipids and its effect on cell polarization, and found that DEX plays a role in promoting the remodeling of microglia from M1 phenotype to M2 phenotype. DEX can down-regulate the expression of M1 marker gene and up-regulate the expression of M2 marker gene, showing anti-inflammatory properties, which is related to the activation of Akt[33]. This result is consistent with the findings of Wang N, Nie H, Zhang Y, etal.[34]. The role of Nrf2/HO-1 pathway and NLRP3 inflammasome are described to protect ischemic brain injury.

2.7 Regulate the content of neuron specific enolase and central nervous system specific protein S100β

Enolase is involved in the ninth step of the glycolysis pathway, which dehydrates 2-phosphoglycerate to form phosphoenolpyruvate (PEP).The enzyme consists of α, β and γ subunits and consists of five isoenzymes, namely αα, ββ, γγ, αβ and αγ, among which γγ-type Enolase is called neuron Specific enolase (NSE) because of its specific location in neurons and neuroendocrine cells.At present, this is the only biochemical marker that can specifically reflect neuronal injury, and its content in brain is the highest[35-36].The amount in normal circulating blood is very small, about 3-8 ng/ml, and the amount in the brain is 30-50 times higher than that in the red blood cells. When ischemic and hypoxic encephalopathy or traumatic brain injury occurs, the nerve cells are seriously damaged or necrotic, the integrity of the cell membrane is destroyed, and NSE is released from the cell membrane and released into the plasma through the damaged blood-brain barrier. Clinically, the plasma NSE content can be measured to speculate whether the brain pathological damage has occurred, and further evaluate the prognosis of the patient.

S-100β is a glial cell marker protein, which is related to its proliferation and differentiation, and can affect human learning and memory ability. It is believed that when cells of the central nervous system are damaged, S-100β protein oozes from the cellular fluid into the cerebrospinal fluid (CSF) and re-enters the bloodstream through the damaged blood-brain barrier.

It has been reported in the literature that changes in the level of NSE combined with the central nervous system specific protein S-100β can reflect the prognosis and severity of brain injury[37].For elderly patients undergoing abdominal surgery, both NSE and S100β were significantly increased in postoperative serum detection, which was speculated to be related to surgical procedures and drugs. By reducing the contents of the first two, DEX has revealed the mechanism by which DEX may play a role in preventing POCD through neuroprotection[38].Li Y et al.[39] found through clinical studies in patients with multiple injuries that S-100β and NSE levels were significantly decreased in the DEX treatment group compared with the conventional treatment group, which seemed to be related to the decreased occurrence of delirium in the dexmedetomidine group.

3. Conclusion

The effects of dexmedetomidine as a neuroprotective agent are mostly limited to animal experimental models and few clinical studies have been conducted. Even in the former, the neuroprotective mechanisms involve only α2A receptors (such as inhibition of glutamic acid, central and peripheral catecholamines release, anti-apoptosis and autophagy), imidazoline receptor-related, and other pathways of action. Through continuous research, the neuroprotective mechanism of DEX becomes clear and its application is gradually widespread. It is expected to continuously make up for the shortcomings of other anesthetic drugs in nerve damage and escort clinical anesthesia.

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