Anticonvulsant and Neuroprotective Effects of Dexmedetomidine on Pilocarpine-Induced Status Epilepticus in Rats Using a Metabolomics Approach

Background: Status epilepticus (SE) is the most extreme form of seizure. It is a medical and neurological emergency that requires prompt and appropriate treatment and early neuroprotection. Dexmedetomidine (DEX) is mainly used for its sedative, analgesic, anxiolytic, and neuroprotective effects with light respiratory depression. The purpose of this study was to comprehensively analyze the metabolic events associated with anticonvulsional and neuroprotection of DEX on pilocarpine-induced status epilepticus rats by LC-MS/MS-based on metabolomics methods combined with histopathology.

Material/Methods: In this research, rats were divided into 3 groups: a normal group, an SE group, and an SE+DEX group. Hippocampus of rats from each group were collected for further LC-MS/MS-based metabolomic analysis. We collected brains for HE staining and Nissl staining. Multivariate analysis and KEGG enrichment analysis were performed.

Results: Results of metabolic profiles of the hippocampus tissues of rats proved that dexmedetomidine relieved rats suffering from the status epilepticus by restoring the damaged neuromodulatory metabolism and neurotransmitters, reducing the disturbance in energy, improving oxidative stress, and alleviating nucleic acid metabolism and amino acid in pilocarpine-induced status epilepticus rats.

Conclusions: This integral metabolomics research provides an extremely effective method to access the therapeutic effects of DEX. This research will further development of new treats for status epilepticus and provide new insights into the anticonvulsional and neuroprotective effects of DEX on status epilepticus.

MeSH Keywords: Dexmedetomidine • Metabolomics • Status Epilepticus

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Background

Status epilepticus (SE) is the most extreme form of seizure, with abnormal discharge of brain neurons that can change behavior, sensation, and consciousness. The adverse consequences of epileptic seizure are generally neurological deficits, cognitive disorder [1], hippocampal damage, high mortality, and brain edema and ischemia [2]. Therefore, timely, appropriate treatment and early neuroprotective measures are needed to address this neurological emergency. Status epilepticus is associated in insufficient cerebral blood flow, excessive energy consumption, glutamate-mediated excitotoxicity, and destruction of neurotransmitter and neuromodulator metabolism [3]. In clinical practice, intravenous diazepam alone or together with phentoin, fosphenytoin, and propofol is the standard first-line therapy [4]. In some cases, however, SE rapidly progresses to the refractory stage with prolonged duration [5], and an increased dosage of medication has been associated with adverse effects such as dose-dependent respiratory suppression and hemodynamic changes [6]. Given the high mortality rate of patients with refractory SE, alternative treatments aimed at different targets are needed to alleviate the pathophysiological process.

Dexmedetomidine (DEX), a highly specific central α2-adrenergic agonist with minimal influence on respiration and hemodynamics [7], has been used in clinical practice for sedation and analgesia, as well as an anxiolytic. DEX can increase the convulsive threshold in cocaine-injected rats [8] and dose-dependently attenuates ropivacaine-induced seizures and negative emotions [9]. In addition, DEX provides neuroprotection against ischemic brain injury by anti-oxidative stress, anti-apoptosis, and inhibiting calcium overload [10]. However, it remains unclear whether DEX is neuroprotective in SE, although DEX had an anticonvulsant effect in a rat model of self-sustaining status epilepticus [11]. The rat SE model induced by lithium-pilocarpine is highly reproducible, with a relatively fixed onset time and a long duration, similar to the human SE formation process, and is one of the more ideal human SE models [12].

Metabolomics has been widely used in the identification of endogenous metabolites. With the rapid expansion of analysis instrument, there are several analytical approaches available for the study of metabolomics, including liquid chromatography/mass spectrometry (LC/MS), gas chromatography/mass spectrometry (GC/MS), and nuclear magnetic resonance (NMR). In the present study, we first assessed the therapeutic effects of DEX on pilo-induced status epilepticus by using an LC-MS-based metabolomics method. Metabolic profiles were analyzed by multivariate analysis techniques, such as clustering analysis, OPLS-DA, and Volcano Plot. Analysis of significant different metabolomics revealed that there are dramatic changes in various small molecule metabolites in the mouse brain, including stress-reactive oxygen species (ROS), disorders of neurotransmitters and neuromodulators, and disturbances in metabolism of energy substances, nucleic acids, and amino acids. KEGG enrichment revealed the metabolic pathways involved in the anticonvulsant and brain-protective effects of DEX. This research provided clues for further in-depth SE research and therapy.

Material and Methods

Experimental design

Sprague-Dawley (SD) rats (20 days old, SPF, 40–50 g) were randomly divided into 3 groups: a normal group, an SE group, and an SE+DEX group (n=10). Diazepam was used in the experimental groups to stop convulsions, while rats in the normal group were treated with the same volume of normal saline (NS). The rats in the SE+DEX group were intraperitoneally injected with DEX (0.2 μg/g) at 60 min, 12 h, 24 h, and 48 h, after SE induction was successfully established. The rats were sacrificed by sodium pentobarbital at 72 h after SE induction, for subsequent experiments. The hippocampal tissues were obtained and rapidly cooled in liquid nitrogen after washing with pre-cooled phosphate-buffered saline (PBS), and then stored at -80°C. Collected samples were transported on dry ice to Shanghai Applied Protein Technology for further metabolomics investigation (Figure 1). Whole brains of rats from each group (n=3) were collected and then fixed in 4% paraformaldehyde and stored at 4°C for further staining. The rats that died or in which SE was not successfully established during the experiments were eliminated from the study and then newly-established SE rats were added.

Status epilepticus rat model

All the rats used in this study were provided by Chongqing Medical University. All the experiments were performed in Day 0

- 18-20 h
- 30 min
- 2 h
- 24 h
- Sampling for metabolomics

Figure 1. Experimental design sketch of this research. Status epilepticus model was established using LCI-Pilo induction, and DEX delivery at 60 min, 12 h, 24 h and 48 h after the onset of SE. LICI, lithium chloride; SE, status epilepticus; Diz, diazepam; DEX, Dexmedetomidine.
Results

Histopathologic characteristics

HE staining revealed compromised structural integrity of the hippocampal CA1 regions in rats in the SE group. The cells exhibited degeneration, liquefaction, and necrosis. Moreover, the structure of granulosa cells was incomplete, and the arrangement of the cells was sparse. However, SE rats treated with DEX exhibited partly intact rat hippocampal CA1 regions (Figure 2A).

Identification of metabolites

As shown in Figure 3, total ion current chromatograms of metabolites were detected using a solvent system. Accordingly, the relative intensity and peaks under positive mode (Figure 3A) and negative mode (Figure 3B) were different. Nevertheless, we did not observe any obvious differences between QCs, suggesting that variation remained in the optimal range.

Furthermore, the metabolomic data was analyzed by PCA (Figure 4). PCA scatter plots showed a distinct segregation of samples between Nor and SE or SE+DEX. However, a large overlap was found between SE and SE+DEX, indicating a minor influence of DEX on metabolic status from SE.

OPLS-DA analysis, served as a supervised method for pattern recognition, was performed on the data in the comparison of SE vs. Nor, SE+DEX vs. SE, and SE+DEX vs. Nor. As shown in Figure 5, groups positive for Nor, SE, and DEX were separated in the OPLS-DA score plots (Figure 5A, 5C, 5E) with a satisfactory goodness of fit (R²=0.997, Q²=0.86 (Figure 5B); R²=0.923, Q²=0.699 (Figure 5D); R²=0.999, Q²=0.426 (Figure 5F)).
For the metabolites detected under negative mode, score plots for each comparison were also presented as separated clusters (Figure 6A, 6C, 6E), along with optimal goodness of fit \(R^2=0.898, Q^2=0.763\) (Figure 6B); \(R^2=0.873, Q^2=0.594\) (Figure 6D); \(R^2=0.847, Q^2=0.164\) (Figure 6F)).
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We found that levels of ADP, R-5-P, Adenosine, F-6-P, GPC, G-6-P, M-6-P, NANA, and G-1-P were higher in the SE group compared with the Nor group. Meanwhile, ADP, R-5-P, Adenosine, F-6-P, GPC, M-6-P, and G-1-P were also detected at higher levels in the SE+DEX group compared to the Nor group. We found that the fold change induced by SE was attenuated by DEX. DEX also suppressed NANA to a normal level, as is shown in comparison of SE+DEX vs. Nor. A significant downregulation of ARA was found in the SE group compared with the Nor group, but the fold change induced by SE compared with Nor was obviously reversed by DEX, showing a decrease of fold change when compared with SE+DEX and Nor (Figure 8B).

Lactate and Alpha-D-Glucose were higher in the SE group compared with the Nor group. IMP, AMP, and glyoxylate were downregulated in the SE+DEX group, in contrast to the Nor and SE groups. We found that DHA and NA6P decreased in the SE group compared with the Nor group, but afterwards it was elevated by DEX in the SE+DEX group but not in the SE group. Choline histidine, acetylcholine, deoxyctydine, and threonine were suppressed by DEX in SE rats in comparison with SE (Figure 8C).

KEGG analysis

To reveal the underlying mechanism of SE induced by pilocarpine and ameliorated by DEX, we performed KEGG enrichment analysis. As mentioned above, pilocarpine administration can lead to a pathological alteration compared with normal animals. As Figure 9 shows, several pathways are involved. Compared with Nor, Purine metabolism, taurine and hypotaurine metabolism, D-Glutamine and D-glutamate metabolism, GABAergic synapse, long-term depression, FoxO signaling pathway, Fructose and mannose metabolism, and central carbon metabolism in cancer I were enriched in the SE group (Figure 9A). Interestingly, most of the pathways, like long-term depression, GABAergic synapse, Glutathione metabolism, FoxO signaling pathway, and central carbon metabolism in cancer, were also matched in the comparison of SE+DEX vs. Nor or SE+DEX vs. SE (Figure 9B, 9C).
Discussion

Status epilepticus (SE) is one of the most common neurological emergencies in children. Traditionally, SE has been defined as a single epileptic seizure lasting more than 30 min or recurrent seizures without regaining consciousness between seizures for greater than 30 min [15]. Currently, the definition of the duration tends to be shortened to 5 min, emphasizing the importance of early treatment [15–18]. The latency of status epilepticus induced by pilocarpine is generally short and often accompanied by cognitive impairment and behavioral abnormalities. Therefore, the pilocarpine-induced SE model has been widely accepted by researchers since it can mimic the clinical characteristics of humans in studies of antiepileptic drugs [12]. In the present study, for the first time, dexmedetomidine was used to interfere with a pilocarpine-induced SE model to investigate the anticonvulsant effect and brain-protection effect of dexmedetomidine, a highly selective a2 receptor blocker, on status epilepticus, characterized by an obvious pathological change observed by HE and Nissl staining. This study has

![Figure 5](image-url). OPLS-DA analysis of LC/MS data from SE vs. Nor (A, B), SE+DEX vs. Nor (C, D), and SE+DEX vs. SE (E, F) under positive mode. Identified compounds could be separated well with optimal goodness of fit. A, C, E: OPLS-DA score plot. B, D, F: Validated model plots obtained by permutation test.
important clinical significance and provides new ideas for status epilepticus therapy. LC/MS-based metabolomics is an effective tool for the detection and identification of biomarkers after stimulation of cells or organisms [19]. In this study, we conducted sample preparation, QC examination, LC-MS/MS mass spectrometry, data pretreatment (peak recognition, peak alignment, peak matching), statistical analysis (PCA, PLS-DA, OPLS-DA, t test), differential compound screening and identification, and bioinformatics analysis to explore the therapeutic effect of DEX on SE. In this study, obvious separation was found between SE vs. Nor and SE+DEX vs. SE (Figures 3–5). However, there was overlap between SE+DEX and Nor or SE+DEX and SE, suggesting DEX might not completely reverse all the SE-induced abnormalities. These observations provide important insights into the novel role of DEX in SE therapy and clinical instructions for further research.

Persistently discharge in neurons in SE can increase cerebral metabolic rate, oxygen consumption, and glucose uptake [20], as well as excess excitatory amino acids release [21,22], creating...
Figure 7. The clustering results of hierarchical cluster analysis based on the significantly different metabolites between groups under positive and negative modes. (A, C, E) Show cluster results of SE vs. Nor, SE+DEX vs. Nor, and SE+DEX vs. SE, respectively, under positive mode; (B, D, F) Show cluster results of SE vs. Nor, SE+DEX vs. Nor, and SE+DEX vs. SE, respectively, under negative mode.
Table 1. Identified significant different metabolites from different groups with the VIP and P value.

| Description       | VIP     | FC     | p value | Description       | VIP     | FC     | p value | Description       | VIP     | FC     | p value |
|-------------------|---------|--------|---------|-------------------|---------|--------|---------|-------------------|---------|--------|---------|
| DHAP              | 2.07    | 1.84   | ***     | DHAP              | 2.04    | 1.55   | ***     | DHAP              | 1.53    | 0.84   |         |
| F-1,6-BP          | 3.82    | 2.20   | **      | F-1,6-BP          | 2.76    | 1.59   | *       | F-1,6-BP          | 3.24    | 0.69   |         |
| Glutamate         | 3.54    | 1.14   |         | Glutamate         | 4.11    | 1.10   |         | Glutamate         | 1.38    | 0.84   |         |
| AR                | 7.92    | 1.62   | ***     | AR                | 6.005   | 1.34   | **      | AR                | 5.35    | 0.83   | *       |
| GSSG              | 1.52    | 1.18   |         | GSSG              | 1.45    | 0.77   | **      | GSSG              | 3.58    | 0.71   | **      |
| Inosine           | 4.82    | 1.54   | *       | Inosine           | 7.57    | 1.16   | *       | Inosine           | 4.26    | 0.87   |         |
| Taurine           | 1.76    | 0.91   |         | Taurine           | 5.80    | 0.86   | **      | Taurine           | 4.39    | 0.92   |         |
| Guanidinobutyric  | 2.37    | 0.72   | **      | Guanidinobutyric  | 3.10    | 0.58   | ***     | Guanidinobutyric  | 1.76    | 0.80   | *       |
| SOPC              | 1.36    | 0.58   | *       | SOPC              | 1.46    | 0.87   |         | SOPC              | 6.61    | 0.57   | **      |
| Hypoxanthine      | 11.78   | 0.87   |         | Hypoxanthine      | 6.90    | 1.17   |         | Hypoxanthine      | 5.40    | 0.89   |         |
| PC (16:0/16:0)    | 1.58    | 0.73   |         | PC (16:0/16:0)    | 1.19    | 0.76   | *       | LysoPC(14:0)      | 1.39    | 0.78   |         |
| ARA               | 23.45   | 0.63   | ***     | ARA               | 21.28   | 0.69   | ***     | ARA               | 21.28   | 0.69   | ***     |
| ADP               | 1.11    | 1.73   | ***     | ADP               | 1.02    | 1.54   | **      | Glyoxylate        | 1.96    | 0.74   |         |
| R-5-P             | 1.70    | 2.51   | **      | R-5-P             | 1.69    | 2.02   | *       | NA6P              | 2.12    | 2.42   | *       |
| Adenosine         | 1.27    | 1.59   | *       | Adenosine         | 1.47    | 1.51   | ***     | Threonate         | 2.92    | 0.70   |         |
| F-6-P             | 2.36    | 2.45   |         | F-6-P             | 3.31    | 2.14   | *       | Choline           | 2.30    | 0.78   | *       |
| GPC               | 7.33    | 3.33   | **      | GPC               | 8.37    | 3.26   | ***     | Histidine         | 2.46    | 0.73   | *       |
| G-6-P             | 2.29    | 1.72   |         | G-6-P             | 1.33    | 2.49   | *       | Acetylcholine     | 2.13    | 0.77   |         |
| M-6-P             | 2.78    | 2.42   |         | M-6-P             | 1.99    | 1.89   | *       | Deoxyctydine      | 1.30    | 0.69   | ***     |
| NANA              | 1.04    | 2.09   |         | NANA              | 1.43    | 0.83   | *       |                   |         |        |         |
| G-1-P             | 2.76    | 2.17   |         | G-1-P             | 1.48    | 1.47   | **      |                   |         |        |         |
| Glutamine         | 3.90    | 1.15   |         | NAAG              | 2.57    | 0.84   |         |                   |         |        |         |
| Glucose           | 1.05    | 4.23   | *       | IMP               | 1.31    | 0.58   | **      | IMP               | 2.10    | 0.63   | ***     |
| Lactate           | 1.57    | 1.35   | *       | AMP               | 1.09    | 0.75   | *       | AMP               | 1.50    | 0.81   | *       |
| DHA               | 2.81    | 0.91   |         | DHA               | 4.50    | 1.12   |         |                   |         |        |         |
| MA                | 2.43    | 1.17   | *       | Glyoxylate        | 2.18    | 0.51   | **      |                   |         |        |         |

GSSG – glutathione disulfide; DHAP – dihydroxyacetone phosphate; ARA – arachidonic acid; DHA – docosahexaenoic acid; ADP – adenosine 5’-diphosphate; IMP – inosine 5’-monophosphate; AMP – adenosine monophosphate; SOPC – 1-Stearyl-2-oleoyl-sn-glycerol 3-phosphocholine; F-1,6-BP – fructose 1,6-bisphosphate; NANA – N-acetyl-D-glucosamine 6-phosphate; MA – malic acid; FC – fold change; * P<0.05, ** p<0.01, *** p<0.001 vs. groups.

an imbalance with inhibitory neurotransmitters, and causing excitotoxicity [23], oxidative stress [24], calcium overload [25], neuronal apoptosis [26], and other brain damage. In this study, the excitatory amino acid glutamine, was significantly increased in the SE group compared with that in the normal group, while taurine, an inhibitory neurotransmitter [27], was significantly reduced, and the high energy metabolism and oxidative stress [28] markers, such as DHAP, F-1,6-BP, AR, GSSG,
inosine, ADP, R-5-P, Adenosine, F-6-P, GPC, G-6-P, M-6-P, NANA, G-1-P, Lactate, Alpha-D-Glucose, and MA, were significantly increased. Guanidinobutyric acid is a precursor of L-arginine, which was significantly reduced in the model group and is associated with the synthesis of the NO in the brain [29]. The alteration of guanidino butyric acid observed in this study suggests that SE causes brain damage by inhibiting the synthesis of NO, similar to the findings of a previous study [30]. SOPC, hypoxanthine [31], and PC (16:0/16:0) [32] are involved in the synthesis of sphingolipids, and are also involved in cell growth, differentiation, and apoptosis, which is important in ensuring the integrity of cell membranes. In this study, there was a significant decrease of these metabolites in the model group, suggesting neuronal apoptosis or death in SE might be caused by SOPC, hypoxanthine, and PC (16:0/16:0). ARA and DHA are brain-protective substances that are indispensable for brain and nerve development [33,34], and these 2 metabolins were significantly reduced in the model group, suggesting cognitive impairment in animals in the model group. These changes were similar to the pathophysiological changes that occurred in animals treated with dexamethasone (SE+DEX). The fold change plots of these significantly different metabolites between groups are shown in Figure 8. (A) Shows metabolites with significant difference between SE and Nor. (B) Shows metabolites with significant difference between SE+DEX and Nor. (C) Shows metabolites with significant difference between SE+DEX and SE.

Figure 8. Significantly different metabolites between groups plotted with fold change plots based on p<0.05 and VIP >1. (A) Shows metabolites with significant difference between SE and Nor. (B) Shows metabolites with significant difference between SE+DEX and Nor. (C) Shows metabolites with significant difference between SE+DEX and SE.
Figure 9. Enriched KEGG pathways based on significant different metabolites between SE and Nor (A), SE+DEX and Nor (B), and SE+DEX and SE (C). Purine metabolism, Taurine and hypotaurine metabolism, D-glutamine and D-glutamate metabolism, GABAergic synapse, and long-term depression were involved in rats with SE, and DEX can restore the symptoms through those pathways.

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during status epilepticus, demonstrating the successful establishment of the model.

DEX has been proved to function on anti-oxidative stress and inhibit glutamate release, resisting epilepsy, and protecting the brain against SSSE [11]. In this study, our observation of DEX delivery confirmed this. DEX-intervention can modulate the level of glutamate, DHAP, F-1,6-BP, AR, GSSG, inosine, ADP, R-5-P, adenosine, F-6-P, GPC, M-6-P, NANA, G-1-P, Guanidinobutyric acid, hypoxanthine, PC (16: 0/16: 0), and ARA, suggesting that after dexmedetomidine intervention, the high post-epileptic metabolic rate, oxidative stress impairment, and neuronal apoptosis were reduced in the model. In addition, changes in excitatory amino acids caused by DEX may also be involved in brain protection and antiepileptic mechanisms. Specifically, the excitatory amino acids such as glutamate and NAAG in SE animals with DEX were significantly lower than those in the model group, and the inhibitory amino acid taurine was also significantly reduced, which may be related to the decrease of glutamate and thus the synthesis of inhibitory amino acids. DEX can increase DHA and NA6P to take part in post-epilepsy brain protection. It suggested that dexmedetomidine’s effect of brain protection was mainly achieved by inhibiting excitatory amino acids. Other indicators of high energy and oxidative stress, such as DHAP, F-1,6-BP, AR, GSSG, and inosine, were significantly reduced compared in the model group, suggesting that DEX attenuated the metabolic rate and oxidative stress injury in the model group.

KEGG is one of the most commonly used bioinformatics databases in the world. It is widely used for understanding advanced function, biological system genome sequencing, and other high-throughput experimental techniques. The results of KEGG enrichments in this study suggest that the pilocarpine-induced epilepticus model led to pathophysiological processes through D-Glutamine and D-glutamate metabolism, alanine, aspartate, and glutamate metabolism, GABAergic synapse, Glutamatergic synapse, and taurine and hypouracine metabolism. Sustained epileptic discharge and neurotoxicity of excitatory amino acids were related to the imbalance between excitatory neurotransmitter and inhibitory neurotransmitter; Central carbon and Choline metabolism in cancer, Glyoxylate and dicarboxylate metabolism, suggesting high metabolism, anaerobic glycolysis, oxidative stress, and other pathophysiological processes of the SE model. Huntington’s disease, Parkinson’s disease, chronic depression, and retrograde endocannabinoid signaling suggest that SE causes brain degenerative changes and changes in cognitive function [35,36]. The reliability of the SE model in this experiment was further confirmed. Comparison of the SE+DEX group with the normal group shows that DEX may play a role by participating in FoxO and other signaling pathways. In addition, FoxO and other signaling pathways were also preconcentrated, suggesting that DEX exerts its therapeutic effect in these ways.

Conclusions

In this study, SE rats were established and subsequently managed with diazepam and DEX. The pathological features of these rats were significantly relieved after treatment with DEX. Our metabolomics approach revealed several compounds – glutamate, GSSG, taurine, and SOPC – involved with balance of excitatory amino acids and regulation of metabolic rate, and these results show the function of DEX in epileptic rats. Observations from the KEGG analysis suggest that DEX plays a role in brain protection and antioxidant stress in the pilo-induced SE model. Future work needs to focus on further characterizing the functions of these metabolites to help develop more effective targets for SE therapy.

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Conflict of interest

None.

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