Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Examination of *ADRB2* gene expression and influence of dexmedetomidine and propofol on hemodynamics after abdominal surgery

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ARTICLE INFO

Original paper

Article history:
Received: November 14, 2022
Accepted: January 11, 2023
Published: January 31, 2023

Keywords:

Dexmedetomidine, propofol, sedation, hemodynamics, bispectral index, Vigileo

ABSTRACT

This study aimed to investigate *ADRB2* gene expression and further understand the effects of dexmedetomidine on cardiac output and oxygen metabolism in tissues and organs by comparing the changes in hemodynamics after the patient has been sedated with dexmedetomidine and propofol after abdominal surgery. A total of 84 patients were randomly divided into the Dexmedetomidine Group (DEX Group with 40 cases) and Propofol Group (PRO Group with 44 cases). For the DEX Group, dexmedetomidine was used for sedation (loading dose: 1 ug/kg, infused for 10min; maintenance dose: 0.3ug/kg/h ~); for the PRO Group, propofol was used for sedation (loading dose: 0.5mg/kg, infused for 10min; maintenance dose: 0.5mg/kg/h ~), and the dosage of sedation drug was according to the sedation target (BIS value 60-80). Before the sedation and 5min, 10min, 30min, 1h, 2h, 4h and 6h after the loading dose, the Mindray and Vigileo monitors were used to record the BIS values and hemodynamics indices of the patients in both groups. Both DEX and PRO groups could reach the target BIS value (P> 0.05). The CI decreases before and after the administration in both groups were significant (P <0.01). The SV level of DEX group after administration was higher than before administration, while the SV level of the PRO Group after administration was lower than before administration (P <0.01). The lactate clearance rate (6h) of DEX Group was higher than that of PRO Group (P <0.05). The incidence of postoperative delirium in the Dexmedetomidine Group was lower than in the Propofol Group (P <0.05). Compared with propofol, dexmedetomidine for sedation can reduce the heart rate and increase the cardiac stroke output. Cell analysis of the *ADRB2* gene showed that this gene is more expressed in the cytosol. Also, its expression in the respiratory system is more than in other organs. Considering that this gene plays a role in stimulating the sympathetic nervous system and the cardiovascular system, it can be used in the safety regulation of clinical prognosis and treatment resistance along with Dexmedetomidine and Propofol.

Doi: http://dx.doi.org/10.14715/cmb/2022.69.1.15

Introduction

The β2 adrenergic receptor is a member of the G protein-coupled receptor superfamily and is expressed in most malignancies. G proteins are protein receptors whose one side is outside the cell and the other side is inside the cell and they cross the membrane and can convert guanosine triphosphate (GTP) to guanosine diphosphate (GDP). This system is a type of messenger for certain chemicals such as hormones and neurotransmitters on the surface of the cell membrane. β2-adrenergic receptors are targeted by various catecholamines, especially norepinephrine, noradrenaline, and epinephrine. Many cells have this type of receptor and when dealing with catecholamine, they stimulate the sympathetic nervous system, and by increasing the level of catecholamine in the blood, it causes the pupils to dilate, focus energy, and direct blood circulation from the organs to the muscles. The β2-adrenergic receptor plays a key role in the sympathetic regulation of the cardiovascular system and mediates vasodilation through the cAMP pathway by stimulating the release of nitric oxide. This receptor is coded by the *ADRB2* gene. Many pieces of evidence show that the ADRB2 gene is effective in regulating immunity, clinical prognosis, and treatment resistance(1-2).

Due to the extensive use of invasive monitoring and treatment in the ICU, the patients often suffer from adverse physiological reactions, such as anxiety, pain and restlessness (3). It also makes patients difficult to tolerate various pipes and treatment measures, leads to unexpected extubation, man-machine confrontation and other adverse events, and increases stress response, finally resulting in poor prognosis. Appropriate analgesia and sedation can reduce the stress response and increase the patient's treatment tolerance (4).

In the past several decades, gamma-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepine drugs) have been the most commonly used sedation drugs in the ICU. However, GABA-mediated sedations often led to complications, such as delirium, respiratory depression and myocardial depression (5); oversedations were very common, patients could not be easily awakened, and it was difficult to assess the degree of se-

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dation. Some serious conditions, such as cerebral hemorrhage, cerebral infarctions and so forth, were delayed, and excessive sedation might also lead to cognitive dysfunction, prolonged application of ventilator, increased pulmonary infection, prolonged hospital stay, etc. (6).

Dexmedetomidine is an α2-adrenergic receptor agonist. Unlike traditional sedation drugs, dexmedetomidine mainly acts on the α2 adrenergic receptors in the cerebral nucleus ceruleus and spinal cord. It has central anti-sympathetic and anxiolytic effects and certain analgesic effects (7-10). It has the following characteristics: It can produce a sedation effect similar to natural sleep. Within a certain range of dosage, the wake system function of the body still exists, so that the patient can be awakened to cooperate with the treatment. Meanwhile, it is beneficial to the evaluation of system function and almost has no inhibitory effect on the breathing of the patient (11, 12). Some studies have shown that it can lower the tracheal intubation rate, shorten the mechanical ventilation time, reduce the incidence of ventilator-associated pneumonia, and shorten the stay in ICU. (13,14). However, some studies have shown that dexmedetomidine has certain adverse effects on the patient's hemodynamics, e.g. causing a decrease in heart rate and blood pressure (15-17), but, there is no relevant study on whether it may cause a decrease in cardiac output and ischemia and hypoxia in tissues and organs while decreasing the heart rate and blood pressure. With critically ill patients who need to be admitted to the ICU after abdominal surgery as the subject, this experiment explored the above-mentioned issues.

Materials and Methods

Subjects

As a prospective, randomized controlled study. The severe patients, who accepted abdominal surgery at the First Affiliated Hospital of Sun Yat-sen University and Huizhou Huiya Hospital of Sun Yat-sen University from May 2018 to June 2021and needed to be transferred to SICU after surgery, were taken as the subjects. Inclusion criteria include 1. ≥ 18 years old; 2. Needed to be transferred to SICU after absolute surgery; 3. Not recovered from anesthesia at the time of transfer, carried tracheal intubation and required mechanical ventilation; 4. The patients or their clients and guardians were informed of and agreed to take part in the experiment; 5. This study has been approved in writing by the Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University and all experiments were performed in accordance with relevant guidelines and regulations by with the Helsinki Declaration. Exclusion criteria include 1. Heart rate <50 beats/min; 2. Circulation was unstable before enrollment and vasoactive drugs were required to maintain blood pressure; 3. The patients were anaphylactic to propofol, dexmedetomidine or relevant ingredients; 4. Pregnancy; 5. The patients participated in other clinical research within 30 days before this study; 6. The patient or his client or guardian refused to participate in the experiment.

Experimental methods

The selected patients were randomly divided into the Dexmedetomidine Group and Propofol Group according to the random data table. The patients of both groups were intravenously infused with Fentanyl for analgesia (loading dose: 0.0007mg/kg, maintenance dose: 0.5ug/kg/h). The patients of DEX Group were intravenously infused with dexmedetomidine for sedation (loading dose: 1 ug/kg, infused for 10min; maintenance dose: 0.3ug/kg/h ~); the patients of PRO Group were intravenously infused with propofol for sedation (loading dose: 0.5mg/kg infused for 10min; maintenance dose: 0.5mg/kg/h ~). The bispectral index monitor (BIS VISTA, Aspect Medical, USA) was used to evaluate the level of sedation, and the dosage of the sedation drugs for both groups was adjusted according to the target sedation level (BIS value 60-80).

Monitoring indicators

Before the sedation and 5min, 10min, 30min, 1h, 2h, 4h and 6h after the loading dose, the BIS values and hemodynamics indices of the patients in both groups were recorded separately (Vigileo, Edwards, USA). Before the sedation and 6h after the sedation, radial arterial blood and central venous blood were collected for blood gas analysis, and the oxygen dynamics indexes were calculated as well. Main observation indicators include: cardiac index (CI), stroke volume (SV), oxygen delivery (DO2), oxygen consumption (VO2) and lactate clearance rate; secondary observation indicators include: heart rate (HR), blood pressure (BP) and systemic vascular resistance (SVR).

ADRB2 gene analysis

First, the ADRB2 gene sequence was extracted from the NCBI database. Then the exact location of this gene was determined using the UCSC database. The OMIM database was used to check the antibodies that bind to the proteins of the target genes. Then cell comparisons were made using the Reactome database and ADRB2 gene expression in different body organs was checked by the Human Protein Atlas database.

Data analysis

In this study, SPSS18.0 software was adopted for data analysis. The measured data were described as mean ± standard deviation ($x \pm s$) and the independent test was adopted for comparison within the group; the continuous data were compared and analyzed between groups by the analysis of variance, and $P < 0.05$ indicated that the difference was statistically significant.

Results

General information (patient characteristics)

In this study, 84 eligible patients were selected, including 18 liver transplantation cases due to liver cirrhosis or liver cancer, 8 cases of gastrointestinal malignant tumor resection, 5 cases of liver cancer resection, 5 cases of retroperitoneal tumor resection, 3 cases of abdominal aortic aneurysm resection, 1 case of pelvic tumor resection, 1 case of common bile duct cancer resection and 1 case of biliary fistula resection; the patients of PRO Group consisted of 10 cases of liver transplantation cases due to liver cirrhosis or liver cancer, 12 cases of gastrointestinal malignant tumor resection, 5 cases of liver cancer resection, 2 cases of retroperitoneal tumor resection, 3 cases of abdominal aortic aneurysm resection, 5 cases of intestinal perforation bowel resection, and 5 cases of pelvic tumor resection. During the study, a liver-transplanted patient in the DEX Group was found to have suffered a major abdo-

Table 1. Comparison of General Information between Both Groups ($\overline{X}$ ±s).

	DEX Group	PRO Group	P
Age (Year)	55±16	55±15	0.990
Sex (M/F)	30/7	26/11	0.650
Weight (kg)	64.9±11.2	64.0±13.3	0.752
APACHE II score	11.0±4.2	10.6±4.5	0.732
BIS score (before sedation)	71.7±12.6	74.4±10.9	0.315

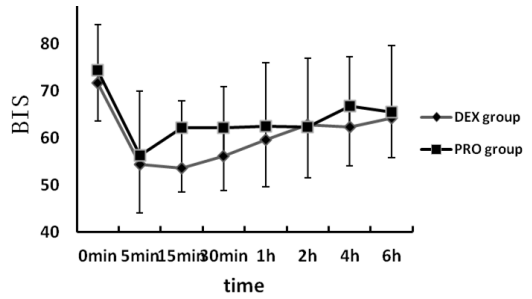

Figure 1. Effects of Dexmedetomidine and Propofol on BIS.

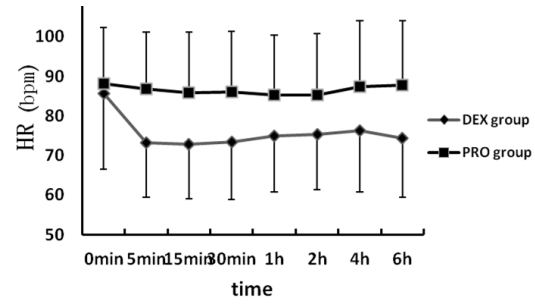

Figure 2. Effects of Dexmedetomidine and Propofol on HR.

minal hemorrhage within 1h after the start of the study and had to be discontinued due to emergency surgery. There were 40 cases in the DEX Group and 44 in the PRO Group. There was no significant difference in disease type, gender, age, weight, acute physiology and chronic health score (APACHE-II) between the two groups of patients (P> 0.05) (Table 1); the difference in sedation level (BIS value) was also not statistically significant in the process of administration (P> 0.05) (Figure 1).

Heart rate and blood pressure

The heart rates of the patients in the DEX Group were significantly lower than the baseline during administration (how much vs. how much, p-value), and the heart rate decreased more significantly after the combined dose than during the maintenance dose (25.25±12.7bpmvs 5.46±11.79bpm, P <0.05). However, the heart rates of the patients in the Propofol Group did not change significantly from the baseline during administration, and its effect on heart rate was smaller than that of dexmedetomidine (72 ± 14 vs 84 ± 15bpm, P = 0.006) (Figure 2).

The blood pressure of the patients in the DEX Group increased significantly after the loading dose but decreased significantly during the maintenance dose when compared with the condition before administration. The blood pressure of the patients in the PRO Group decreased significantly during the loading dose and maintenance dose, but the difference between both groups was not statistically significant (P values were 0.165 and 0.067, respectively) (Figures 3 and 4).

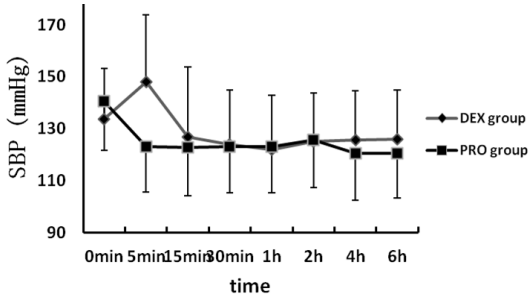

Figure 3. Effects of Dexmedetomidine and Propofol on SBP.

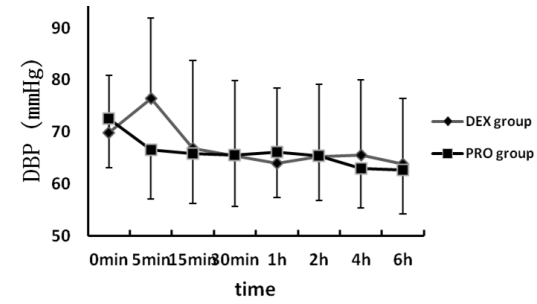

Figure 4. Effects of Dexmedetomidine and Propofol on DBP.

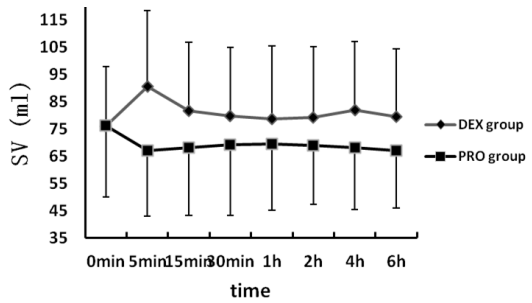

Figure 5. Effects of Dexmedetomidine and Propofol on SV.

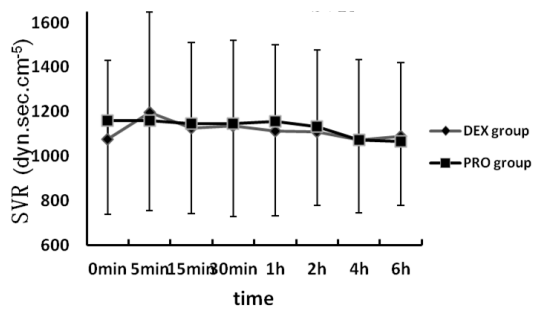

Figure 5. Effects of Dexmedetomidine and Propofol on SVR.

Stroke volume (SV), systemic vascular resistance (SVR) and cardiac index (CI)

SV and SVR of the patients in the DEX Group increased significantly after the loading dose, but decreased significantly from the baseline during the maintenance dose, while SV and SVR of the patients in the PRO Group were significantly higher than the baseline after the loading dose and during the maintenance dose (Figures 5 and 6);

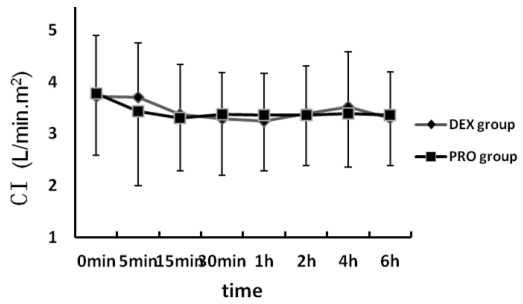

Figure 7. Effects of Dexmedetomidine and Propofol on CI.

meanwhile, during the sedation period, CI was significantly lower than the baseline in both groups, but there was no statistical difference in the decreasing level of CI between both groups (P = 0.545) (Figure 7).

Oxygen delivery, oxygen consumption and lactate clearance rate

Before administration, the oxygen delivery and oxygen consumption were at normal levels and there was no statistical difference in the patients of both groups. 6h after the sedation, the oxygen delivery (DO2) and oxygen consumption of the patients in both groups were significantly lower than those before administration; there was no statistical difference in the changes in oxygen delivery and oxygen consumption between both groups. Meanwhile, the lactate level in the Dexmedetomidine Group was significantly lower than in the Propofol Group, and the lactate clearance rate after 6h in the Dexmedetomidine Group was significantly higher than in the Propofol Group (50.9 ± 22.2% VS 18.6 ± 36.0% P <0.01). In addition, the blood creatinine – a renal impairment index more sensitive to ischemia and hypoxia - showed no statistical difference before and after the sedation (Table 2).

Liquid balance, urine output

There was no statistical difference in the liquid intake and output at 6 hours between both groups (intake: 1168 ± 373ml VS 1109 ± 470ml P = 0.54) and (output: 834 ± 665ml VS 639 ± 369ml P = 0.130). After 6h observation of the mechanical ventilation (12.3 ± 7.7 VS 21.7 ± 50.7 P = 0.259), the doctors in charge were instructed to adjust DEX or PRO according to the condition until discontinuing them. Finally, the ICU stays in both groups (1.5 ± 1.1 VS 1.7 ± 2.1 P = 0.552) were not statistically different (Table 3).

Incidence of postoperative delirium

The incidence of postoperative delirium in the Dexmedetomidine Group was significantly lower than in the Propofol Group (7.5% VS 29.5% P <0.05) (Table 4).

Cellular analysis and *ADRB2* gene expression

The cellular analysis of the *ADRB2* gene by antibodies that bind to the proteins of target genes showed that the protein encoded by the *ADRB2* gene is present in the cytosol in a larger quantity. Also, the examination of gene expression in different organs of the body showed the expression of the *ADRB2* gene in the respiratory system, skin, and

Figure 8. Examining *ADRB2* gene expression in different body organs.

Table 2. Effects of Dexmedetomidine and Propofol on oxygen metabolism in organs.

Group	DO2 (ml.min^{-1}.m^{-2})		VO2 (ml.min^{-1}.m^{-2})		Creatinine		6H lactate clearance rate (%)
	T1	T2	T1	T2	T1	T2	
DEX	612±79	485±88[a]	230±24	165±18[a]	88±12	78±16	50.9±22.2[b]
PRO	625±98	498±101[a]	218±19	158±23[a]	96±21	89±25	18.6±36.0

Note: T1 - before sedation, T2 - 6 h after sedation, a - P <0.05 while compared with the condition before administration in the same group, b - p <0.05 while compared with the control group at the same point.

Table 3. Effects of Dexmedetomidine and Propofol on liquid intake/output, mechanical ventilation and hospital stay.

	Dex Group	PRO Group	P
6h intake (ml)	1168±373ml	1109±470ml	0.54
6h output (ml)	834±665ml	639±369ml	0.130
Mechanical ventilation (h)	12.3±7.7	21.7±50.7	0.259
ICU stay (day)	1.5±1.1	1.7±2.1	0.552

Table 4. Effects of dexmedetomidine and propofol on the incidence of delirium after abdominal surgery.

	Delirium incidence [n (%)]				
Group	T1	T2	T3	T4	Total
DEX Group	0	1(2.5)	2(5.0)	0	3(7.5)
PRO Group	0	6(13.6)	5(11.4)	2(4.5)	13(29.5)
P					0.011

connective and soft tissue more than in other organs and the eye, pancreas, and endocrine tissues including the thyroid gland, the parathyroid gland, the adrenal gland, and the pituitary gland less than other organs. Gene expression study by microarray expression data also confirmed these findings (Figure 8) (18).

Discussion

This study showed that the patients in the Dexmedetomidine Group had a significantly lower heart rate than those in the Propofol Group during the experiment, which was more pronounced in the patients with tachycardia, and the incidence of bradycardia was not high (3 of 37 patients) and did not need drug intervention. The studies by Tobias and Chrysostomou have pointed out (19-21) that dexmedetomidine could reduce the incidence of ventricular and supraventricular tachycardia and even make the borderline tachycardia cardioversion to the sinus heart rate, which might be related to the inhibition of the sympathetic nerve excitability. Thus, tachycardia patients with stable hemodynamics might benefit more from dexmedetomidine sedation.

We found that, unlike the Propofol Group, the blood pressure of the patients in the Dexmedetomidine Group increased significantly during the loading dose, but decreased significantly during the maintenance dose. Makaritsis(22) et al. pointed out that high doses of α2 receptor agonists dominated the role of α2B receptors on the smooth muscle of the resistance vessel, which might cause a rise in blood pressure, and some scholars even believed that it might be the pathogenesis of essential hypertension. The study of Ebert et al. on dexmedetomidine (23) also pointed out that the low-dose (0.25–1 mg/kg) load would lead to a decrease in blood pressure and cardiac output, while a higher loading dose (1–4 mg/kg) might cause the rise of blood pressure and the reflex bradycardia. In this experiment, the dose for the patients in the Dexmedetomidine Group was same with Gerlach et al (24) results. Therefore, for patients with unstable blood pressure, we could slow down the infusing speed of the loading dose to avoid sharp fluctuation of blood pressure.

The animal studies by Lee et al. (25) showed that dexmedetomidine could offset the decrease of cardiac output caused by slowing heart rate by increasing systemic vascular resistance and cardiac contractile function. Similarly, we found that the heart rate slowing of the patients in Dexmedetomidine Group was accompanied by the increase of peripheral vascular resistance and stroke volume (SV), which was more pronounced after the loading dose. The increase of SV also suggested that dexmedetomidine sedation might have the effect of enhancing myocardial contractility, but its mechanism should be further researched.

Dexmedetomidine not only exerted sedation, hypnosis and anxiety resistance through the α2A receptor of the nucleus ceruleus of the brainstem but also could inhibit the activity of peripheral sympathetic nerves and accordingly reduce the secretion of norepinephrine and epinephrine (26) so that the patient could be in the status of the systematic sympathetic nerve suppression. Other studies have shown that (27) dexmedetomidine could also reduce the oxidative stress and inflammatory response of the body. These effects could significantly reduce the need for oxygen supply in patients, lighten the sensitivity of tissues and organs to ischemia and hypoxia and play a role in protecting organ functions. Fuhai Ji et al. pointed out that the application of dexmedetomidine could significantly reduce the incidence of acute kidney injury in patients after cardiac surgery, and inhibit the expression of P38 mitogen-activated protein kinase (P38-MAPK) and thioredoxin-interacting protein (TXNIP), which had renal protection for ischemia-reperfusion injury in the diabetic nephropathy mouse model (28, 29). The results of this study also showed that oxygen consumption also decreased synchronously along with the significant decrease of oxygen delivery. Finally, the patients did not show any signs of tissue and organ ischemia and hypoxia: there was no obvious abnormality in renal function, the level of lactic acid was normal, and the lactate clearance rate was also higher than that of the Propofol Group.

Dexmedetomidine can cause a slowing of heart rate and dropping of blood pressure and more liquid or vasoactive drugs may be needed clinically. Due to the short research period, no significant increase in liquid demand and application of vasoactive drugs was found in this study, the 6h liquid demand was equivalent, and the output of Dexmedetomidine Group was even more than Propofol Group. So, the difference between both groups was not statistically significant. Compared with the Propofol Group, the total average time of dependence on the ventilator and the stay in ICU was much shorter (although the difference was not statistically significant), which indicated that dexmedetomidine was safer and more effective in these patients.

Various studies indicate the effects of adrenergic receptors on neuronal excitability and sympathetic regulation of the cardiovascular system. It seems that in general, beta-adrenergic receptors increase the release of glutamate and increase neurogenesis, causing an increase in neuronal excitability and induction of long-term strengthening in brain synapses, which play an effective role in the anesthesia system. However, the role of adrenergic receptors in the changes caused by the cardiovascular system and synaptic plasticity is still not well known and should be given more attention in future research.

Limitation

As the research duration was too short, this study was difficult to assess the impact on the long-term prognosis of the patients.

Conclusion

Dexmedetomidine can significantly lower the heart rhythm of patients with abdominal surgery, but its effect on cardiac output and oxygen metabolism is not significantly different from propofol.

Consent for publication

Not Applicable.

Availability of data

All data generated or analyzed during this study are included in this article.

Competing interests

None of the authors declare any competing interests.

Conflicts of Interest

The authors have nothing to declare under this clause.

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