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Research Article
Anticonvulsant and Proconvulsant Effects of Trazodone in Different Seizure Models

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Abstract

Background and Objective: Increasing patients with epilepsy need some form of antidepressant, which trazodone is one of the most widely prescribed. However, the seizure risk of trazodone has not been assessed. The objective of this study is to determine whether trazodone hydrochloride (TH, a 5-HT antagonist/reuptake inhibitor) has anticonvulsant and pro-convulsant effects. **Materials and Methods:** Electroconvulsions and four chemicals (pentylenetetrazole, 3-mercaptopropionic acid, thiosemicarbazide and bicuculline) were used to induce seizures in animal models. Effects of the acute treatment with TH on the anticonvulsant action of three common antiepileptic drugs against the maximal electroshock (MES) test in mice were investigated. **Results:** In the MES model, protection effects were observed for the chronic but not acute treatment with TH. In chemicals, induced seizures models, the acute treatment with TH did not show anticonvulsant and proconvulsant effects in 3-mercaptopropionic acid, thiosemicarbazide and bicuculline-induced seizure models. While it showed proconvulsant effects in the PTZ model, exacerbating the convulsion and death at a dose of 100 mg kg^{-1} singly administered. In the test to ascertain the effect of TH on the anti-MES action of three antiepileptics, the anticonvulsant effect of valproate was enhanced through the single administration of TH. While the anti-MES activity of carbamazepine and oxcarbazepine was weakened by acute TH when applied with a clinical dose or higher. **Conclusion:** The obtained results suggested that the TH has no anticonvulsant and proconvulsant effects under the clinic dosage but it can interfere with the anticonvulsive action of other antiepileptic drugs when combined.

Key words: Trazodone, epilepsy, seizure, antiepileptic drugs, anticonvulsive, proconvulsant, maximal electroshock

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Recently, epilepsy and depression coexist commonly. About 55% of patients with epilepsy suffered from depression[1,2]. Depression in some cases may be due to the social discrimination and stigma imposed by recurrent seizures[3]. In turn, depression can directly increase seizure frequency through the mechanism of sleep deprivation[4]. And increasing scientific research indicates that depression shares common pathophysiologic mechanisms with epilepsy[5-7]. In a word, more and more patients with epilepsy need some form of antidepressant. Therefore, it is important to prescribe appropriate antidepressants for these patients with epilepsy. The choice needs more and better information concerning these drugs, especially the information on safety and effects on seizures.

To date, many antidepressants have been reported to induce or inhibit seizures clinically or experimentally[8-11]. In the past, tricyclic antidepressant drugs were reported to induce seizures in some cases[12,13]. Since these drugs shared a common mechanism i.e. blocking the reuptake of norepinephrine and serotonin, many clinicians were convinced that the mechanism is involved in the seizures and avoided prescribing these drugs to patients with epilepsy. However, more and more human studies and animal data indicated that serotonin and norepinephrine play a role as anticonvulsive neurotransmitters[14-16]. Increasing evidence showed that selective serotonin reuptake inhibitors (SSRIs) inhibit both focal and generalized seizures[17,18].

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Trazodone, a serotonin antagonist and reuptake inhibitor, is mostly prescribed for depressive disorder. In 2019, it was the 25th most commonly prescribed medication in the United States, with more than 23 million prescriptions[19]. A few clinic cases reported the proconvulsant effect of trazodone and most of them were under overdose due to its application in clinic form[20-23]. Based on its clinic performance, people prefer to believe that trazodone, just like SSRIs and SNRIs, exhibits a lower seizure risk than others such as tricyclic antidepressants (TCAs). Nevertheless, the seizure risk of trazodone needs more data to assess such as evidence-based medicine data or experimental studies.

The aforementioned results encouraged us to the anticonvulsant and proconvulsant effects of trazodone hydrochloride (TH) in seizure models in mice. The interaction between antidepressants and commonly used antiepileptic drugs (AEDs) is also important for patients with epilepsy. Therefore, the TH was combined with three antiepileptic drugs which commonly used in the clinic and possible synergistic or antagonistic effects were investigated in the maximum electric shock test in mice. The aim of this study was not to search for a novel and effective anticonvulsant agent but to indicate an antidepressant that can be safely used in epileptic patients.

MATERIALS AND METHODS

Study area: This study was carried out at Jinggangshan University, Ji'an City, China, from 2021-July.

Animals and experimental conditions: All experiments were carried out on Kunming mice weighing 18-22 g, half male and half female. A total of 656 mice were used in the whole experiment. Animals were kept in cages and had free access to food and water under standardized living conditions. The animals were tested after 3 days of adaptation to new laboratory conditions. Animal experiments were carried out in accord with the reported guide[24]. The approval from the local ethics committee was also obtained.

Drugs: The following drugs were used in this study: 3-mercaptopropionic acid (3-MP), pentylenetetrazole (PTZ), thiosemicarbazide (TSC) and bicuculline (BIC) were bought from Aladdin Industrial Corporation (Shanghai, China). Carbamazepine (CBZ), Trazodone Hydrochloride (TH), valproate sodium (VPA) and oxcarbazepine (OXC) were purchased from Melongpharma Co., Ltd. (Dalian, China). 3-MP, PTZ, TSC, TH and VPA were dissolved in a 0.9% sodium chloride solution. Dimethyl sulfoxide (DMSO) was used as the vehicle of the CBZ and OXC. A solution of 0.1 N HCl was used to dissolve the BIC, which was diluted with normal saline to the final volume and was used out in half an hour. All drugs were administered intraperitoneally (i.p.) in a volume of 0.1 mL/20 g body weight. TH was administered in a single injection at 30 min before tests in acute treatment, or given once a day for 7 successive days in chronic treatment.

Maximal electroshock test: The maximal electroshock (MES) test is a widely used animal model of tonic-clonic seizure, which can show the efficacy of antiepileptic agents

against partial and generalized seizures[25,26]. In the MES test, seizures in mice were induced by a 60 Hz alternating current with an intensity of 50 mA. An alternating current was applied through the ear clip electrode for 0.2 sec. After electric stimulation, Tonic-Clonic (Grand Mal) seizure could be induced in 100% of mice. Abolition of the hind limb tonic extension spasm was considered the protection of a drug against the MES-induced seizures. In this model, TH was singly injected *i.p.* at the dose levels of 30, 100 and 300 mg kg^{-1} for evaluating its acute anti-MES activity. And effects of the chronic treatment with TH against the seizure induced by electroconvulsive were evaluated after giving TH once a day for 7 successive days at the dose levels of 10, 30 or 100 mg kg^{-1} [27].

Chemical induced seizures tests: Several chemicals, which can induce a seizure, were used to evaluate the efficacy of antiepileptic drugs. Different convulsant chemicals were taken in different doses to obtain the proper seizure proportion. Firstly, PTZ (subcutaneous injection s.c.), 3-MP (i.p.), TSC (i.p.) or BIC (s.c.) was injected individually, 30 min later the vehicle or TH (100 mg kg^{-1}, a safe dose in mice and 8 times the clinic dose) was administered i.p., to mice (groups of ten). The treated mice were placed separately and observed for one hour. The numbers of the clonic seizures (range from violent convulsions of the limbs to exaggerated shaking or vibration of the limbs), tonic seizures (pushing the limbs towards the body and rigidly pushing away from it, usually a maximal extension of the hind leg) and the number of deaths was noted[28].

Tests for the effect of TH on the anti-MES action of three antiepileptics: One hundred and twenty mice were equally divided into 5 groups. Mice in each group were i.p., injected vehicle, 12.5 mg kg^{-1} of TH, 25 mg kg^{-1} of TH, 50 and 100 mg kg^{-1} of TH, respectively. Then the antiepileptic VPA was evaluated for its anti-MES activity using the treated mice 30 min later. Mice were given a range of antiepileptics doses until at least three points were established in the range of 10–90% seizure protection. From the dosage and protection data, the respective ED_{50} values (including the antiepileptics alone and TH combined) and 95% confidence intervals were calculated[27]. The effects of TH on the anti-MES action of CBZ and OXC were also investigated using the same procedure.

Statistics analysis: ED_{50} values with their respective 95% confidence intervals were calculated using log-probit analysis. For the comparison of the ED_{50} value, the standard error (SEM) of the mean values was transformed from 95% confidence intervals and the ED_{50} in different groups were compared and analyzed by the One-Way Analysis of Variance (ANOVA) followed by Dunnett's test. The Fisher's exact test was used to compare and analyze the number and lethality of the seizures in different groups. $p \leq 0.05$ was considered statistically significant. All statistics were operated on GraphPad Prism version 7.0.

RESULTS

Maximal electroshock test: Preliminarily, TH was administered (i.p.) singly at the dose levels of 30, 100 and 300 mg kg^{-1} for evaluating its acute anti-MES activity at 30 min intervals after administration. TH was inactive when administered at the dose of 30 and 100 mg kg^{-1} in the MES test with no mouse protection. At the dose of 300 mg kg^{-1}, four animals died and the rest were induced seizures. Effects of the chronic treatment with TH against the seizure induced by electroconvulsive in mice were observed after giving TH once a day for 7 successive days. Mice who took 10 and 30 mg kg^{-1} of TH were not protected in the MES test. While two mice in six were protected when given the dose of 100 mg kg^{-1}. A bigger dose was not tested because of the death in the single administration at 300 mg kg^{-1}.

Chemical induced convulsions tests: To obtain more information about the anticonvulsant and proconvulsant effects of TH, four chemical-induced convulsions tests were carried out. PTZ has been reported to produce seizures by inhibiting g-aminobutyric acid (GABA) neurotransmission. In the PTZ induced convulsions tests, 25, 50 and 100 mg kg^{-1} of PTZ were injected into mice. The clonic convulsion proportion, as well as the tonic convulsion and death proportion, were listed in Table 1. It can be seen that 50 and 100 mg kg^{-1} of PTZ induced the convulsion in 40 and 100 percent, respectively. The combined treatment with 100 mg kg^{-1} of TH did not relieve the convulsion and death when compared to the single administration of PTZ at 100 mg kg^{-1}. Contrarily, it aggravated the convulsion and death when compared to the single administration of PTZ at 50 mg kg^{-1}. The combined treatment with 25 mg kg^{-1} of TH led to no change in the convulsion and death when compared to the single administration of PTZ at 50 or 100 mg kg^{-1}. These results suggest that TH has no protection for the PTZ induced convulsions, instead, it will exacerbate the convulsion and death when administered at a high dose.

3-MP is a competitive inhibitor of GABA synthase and glutamate decarboxylase. It inhibits the synthesis of GABA and

Table 1: Effects of the acute treatment with trazodone hydrobromide (TH) on the convulsions and the death induced by pentetrazol (PTZ) in mice

Groups (mg kg^{-1})	Clonic convulsion	Tonic convulsion	Death
TH (100)	0/10	0/10	0/10
TH (25)	0/10	0/10	0/10
PTZ (100)	10/10	10/10	9/10
PTZ (50)	4/10	4/10	2/10
PTZ (100)+TH (100)	10/10	10/10	10/10
PTZ (50)+TH (100)	9/10*	9/10$^{\#}$	8/10*
PTZ (100)+TH (25)	10/10	10/10	10/10
PTZ (50)+TH (25)	4/10	5/10	1/10

*p<0.05, when clonic convulsion in group of PTZ (50 mg kg^{-1}) vs. clonic convulsion in group of PTZ (50 mg kg^{-1})+TH (100 mg kg^{-1}), $^{\#}$p<0.05, when tonic convulsion in group of PTZ (50 mg kg^{-1}) vs. tonic convulsion in group of PTZ (50 mg kg^{-1})+TH (100 mg kg^{-1}) and *p<0.05, when death in group of PTZ (50 mg kg^{-1}) vs. death in group of PTZ (50 mg kg^{-1})+TH (100 mg kg^{-1})

Table 2: Effects of the acute treatment with trazodone hydrobromide (TH) on the convulsions and the death induced by 3-Mercaptopropionic acid (3-MP) in mice

Groups (mg kg^{-1})	Clonic convulsion	Tonic convulsion	Death
3-MP (60)	10/10	7/10	10/10
3-MP (30)	6/10	5/10	6/10
3-MP (60)+TH (100)	10/10	8/10	10/10
3-MP (30)+TH (100)	6/10	6/10	5/10
3-MP (60)+TH (25)	10/10	8/10	9/10
3-MP (30)+TH (25)	5/10	5/10	7/10

Results are expressed as the percentage of animals that exhibited clonic convulsion, tonic convulsion and death among all animals tested. The number of animals tested in each group was ten. Statistical analysis of data from this test was performed by using Fisher's exact test

Table 3: Effects of the acute treatment with trazodone hydrobromide (TH) on the convulsions and the death induced by thiosemicarbazide (TSC) in mice

Groups (mg kg^{-1})	Clonic convulsion	Tonic convulsion	Death
TSC (25)	10/10	9/10	9/10
TSC (12.5)	5/10	4/10	4/10
TSC (25)+TH (100)	10/10	10/10	9/10
TSC (12.5)+TH (100)	5/10	5/10	5/10
TSC (25)+TH (25)	10/10	10/10	10/10
TSC (12.5)+TH (25)	6/10	4/10	3/10

Results are expressed as the percentage of animals that exhibited clonic convulsion, tonic convulsion and death among all animals tested. The number of animals tested in each group was ten. Statistical analysis of data from this test was performed by using Fisher's exact test

Table 4: Effects of trazodone hydrobromide (TH) acute treatment on bicuculline (BIC)-induced convulsion and death in mice

Groups (mg kg^{-1})	Clonic convulsion	Tonic convulsion	Death
BIC (2.7)	10/10	10/10	10/10
BIC (1.35)	2/10	3/10	3/10
BIC (2.7)+TH (100)	10/10	9/10	10/10
BIC (1.35)+TH (100)	1/10	2/10	2/10
BIC (2.7)+TH (25)	10/10	10/10	10/10
BIC (1.35)+TH (25)	3/10	4/10	3/10

Data indicate the percentage of animals with clonic convulsions, tonic convulsions and death in the test animals (ten in each group). The Fisher exact test was used to compare and analyse the data from different groups

reduces the level of GABA in the brain. In the 3-MP induced convulsions test (Table 2), 30 and 60 mg kg^{-1} of 3-MP induced the clonic convulsion at 60 and 100 percent, respectively. The combined treatment with 3-MP and TH did not give a significant effect on the tonic convulsion and death when compared to the single administration of 3-MP.

TSC, another competitive inhibitor of GABA synthesis enzyme, can induce convulsions in mice via decreasing GABA levels in the mouse brain. In the TSC induced convulsions test (Table 3), 12.5 and 25 mg kg^{-1} of TSC induced the clonic convulsion at 50 and 100 percent, respectively. The extra administration with 25 or 100 mg kg^{-1} of TH did not relieve single administration of 25 mg kg^{-1} TSC or exacerbate the convulsion and death when compared to the single administration of 12.5 mg kg^{-1} TSC.

BIC, a competitive antagonist of the GABAA receptor, produces convulsions through its antagonism to the GABAA receptor. In the BIC induced convulsions test (Table 4), 2.7 mg kg^{-1} of BIC induced the clonic convulsion, tonic convulsion and death completely. And 1.35 mg kg^{-1} of BIC induced the clonic convulsion, tonic convulsion and death in 20, 30 and 30 percent, respectively. The extra administration

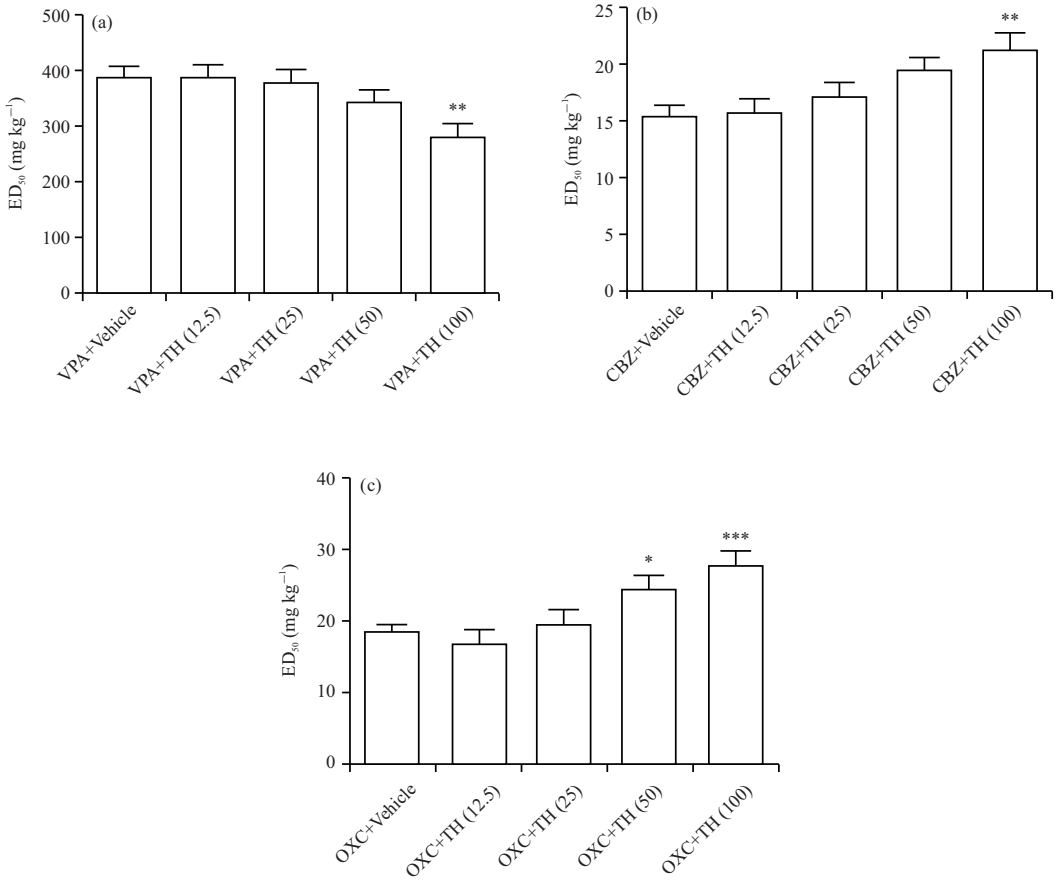

Fig. 1(a-c): Effect of the acute treatment with trazodone hydrobromide (TH) on the anticonvulsant action of (a) valproate-VPA, (b) Carbamazepine-CBZ and (c) Oxcarbazepine-OXC against maximal electroshock-induced seizures in mice
Columns are represented as median effective doses (ED50 and SEM value) in the MES test, antiepileptics were administered i.p. singly half an hour before electroconvulsive, *p<0.05, **p<0.01, ***p<0.001 vs. control (animals treated with an antiepileptic plus saline) and X-axis: Groups

with 25 or 100 mg^{-1} kg^{-1} of TH did not relieve the convulsion and death of mice when compared to the single administration of 2.7 mg kg^{-1} BIC or exacerbate the convulsion and death when compared to the single administration of 1.35 mg kg^{-1} BIC.

Test for the effect of TH on the anti-MES action of three antiepileptics: The effects of TH on the anticonvulsive activity of three common antiepileptics were also evaluated in this study. As shown in Fig. 1a, TH applied at 12.5, 25 and 50 mg kg^{-1} has no significant influence on the anti-MES action of VAP. While TH applied 100 mg kg^{-1} increased the anti-seizure action of VPA in the MES model, decreasing its ED_{50} value from 388.44±20.8-281.57±23.89. As shown in Fig. 1b, TH applied at 12.5, 25, 50 and 100 mg kg^{-1} decreased the anti-MES action of CBZ dose-dependently, though the decline was not significant at the dose of 12.5, 25 and 50 mg kg^{-1}. When TH was applied at 100 mg kg^{-1}, the ED_{50} value of CBZ was increased from 15.61±0.83-21.44±1.49. Resemble CBZ, the anti-MES action of OXC was also decreased when applied TH at 12.5, 25, 50 and 100 mg kg^{-1}. As shown in Fig. 1c, TH applied at 50 and 100 mg kg^{-1} significantly decreased the anti-MES action of OXC, increasing its ED_{50} value from 18.47±1.1-24.94±1.58 and 28.01±2.08 mg kg^{-1}, respectively.

DISCUSSION

Results of this study suggested that the acute treatment of TH did not occur seizures up to lethal dose in mice (i.p., 300 mg kg^{-1}). And it did not lead to the protective effect in the maximal electroshock test in mice up to lethal dose either. However, chronic treatment of TH at 100 mg kg^{-1} showed a protective effect for mice in the maximal electroshock test. This situation is the opposite of fluoxetine. Acute[29], but not chronic treatment of fluoxetine[30] showed anti-MES action in mice. Acute TH did not show the anticonvulsant or

proconvulsant action in the 3-MP, TSC and BIC induced convulsions models. But it showed proconvulsant action in the PTZ induced convulsions model when applied at a high dose (100 mg kg^{-1}). This suggested that TH applied at a high dose might decrease the convulsive threshold induced by PTZ. The above results give a complex conclusion on the anticonvulsant and proconvulsant action of TH. But at least no significant effects of TH on experimental convulsions were certainly observed when applied at 25 mg kg^{-1} or below.

A clinical case supported the possible role of serotonin modulation in Dravet Syndrome patients (severe myoclonic epilepsy in infancy) and gave clinical sustenance to their suggestion that trazodone may be an efficacious agent in these patients[31]. However, it is also shown to have mixed effects on the pharmacodynamics of antiepileptic drugs. Lefkowitz *et al.*[32] reported a case of a patient with new-onset seizures 18 days after trazodone initiation for depression. Hill *et al.* found that the risk for seizures in the first 5 years of follow-up was highest for trazodone in all investigated antidepressant drugs[33]. Based on this uncertainty, more and deeper research needs to be carried out to explain possible underlying causes and obtain the safety of trazodone[34].

The selection of appropriate antidepressants for patients with epilepsy should be based not only on their individual effects in a series of epilepsy models but also on their interaction with antiepileptics. Due to the very limited clinical data, the information on the interaction from experimental research provides important value. In this study, the maximal electroshock model in mice was used to investigate the possible interactions between TH with antiepileptic drugs VPA, CBZ and OXC. TH decreased the anticonvulsive action of VPA at doses ranging from 12.5-100 mg kg^{-1}. In our previous work, we found that SNRIs such as venlafaxine and duloxetine potentiated the action of antiepileptic drugs[35,36]. Acute TCAs such as amitriptyline and imipramine also enhanced the protective action of valproate. The potentiation of TH on the VPA might be attributed to its effect on the concentration of VPA in the brain. Acute and chronic TH (40 mg kg^{-1}) have been reported to increase the brain concentration of VPA[34]. For the antiepileptic drugs CBZ and OXC, acute TH decreased their anti-MES action. This may also be due to the effects of TH on the brain concentration of CBZ and OXC. Similar results have been reported by Borowicz that chronic trazodone (40 mg kg^{-1}) markedly reduced the brain concentrations of CBZ and decreased the anti-MES action of carbamazepine CBZ[37]. TH applied at 50 mg kg^{-1} or higher significantly decreased the anti-MES action of OXC in mice. The dose of 50 mg kg^{-1} used in mice corresponds to the dose of 4 mg kg^{-1} in humans[38], which is also approximately equal to the clinical dose of TH in humans (240 mg day^{-1}). In other words, the clinical dose of TH may markedly weaken the therapeutic effect of OXC for patients with epilepsy.

CONCLUSION

In summary, despite anticonvulsant effects in the MES test being observed for chronic TH, it remained ineffective or even proconvulsant effect in acute PTZ, TSC, 3-MP, BIC and electrically induced seizures. The more important is that TH (applied with a clinical dose or higher) significantly weakens the anticonvulsive activity of antiepileptic drugs CBZ and OXC. These reminded clinicians to be more cautious when prescribing TH to the patient with epilepsy combined with other AEDs.

SIGNIFICANCE STATEMENT

Trazodone is a serotonin antagonist and reuptake inhibitor, which was widely prescribed for depressive disorder. However, little information has been reported on the trazodone in seizures or epileptic patients in the aspect of safety and effects. Therefore, the current study was conducted to investigate the anticonvulsant and proconvulsant effects of trazodone in several screening models of seizures and the interactions between it and common Antiepileptic Drugs (AEDs) *in vivo*. This study provided information for clinicians and patients with epilepsy when using trazodone, especially in terms of security.

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