Casein Kinase II Inhibition Reverses Pain Hypersensitivity and Potentiated Spinal N-Methyl-D-aspartate Receptor Activity Caused by Calcineurin Inhibitor

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ABSTRACT

Clinically used calcineurin inhibitors, including tacrolimus (FK506) and cyclosporine A, can induce calcineurin inhibitor-induced pain syndrome (CIPS), which is characterized as severe pain and pain hypersensitivity. Increased synaptic N-methyl-D-aspartate receptor (NMDAR) activity in the spinal dorsal horn plays a critical role in the development of CIPS. Casein kinase II (CK2), a serine/threonine protein kinase, can regulate synaptic NMDAR activity in the brain. In this study, we determined whether spinal CK2 is involved in increased NMDAR activity and pain hypersensitivity caused by systemic administration of FK506 in rats. FK506 treatment caused a large increase in the amplitude of NMDAR-mediated excitatory postsynaptic currents (EPSCs) evoked by primary afferent stimulation and in the frequency of miniature EPSCs of spinal dorsal horn neurons. CK2 inhibition with either 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole (DRB) or 4,5,6,7-tetrabromobenzotriazole (TBB) completely normalized the amplitude of evoked NMDAR-EPSCs of dorsal horn neurons in FK506-treated rats. In addition, DRB or TBB significantly attenuated the amplitude of NMDAR currents elicited by puff application of N-methyl-D-aspartate to dorsal horn neurons in FK506-treated rats. Furthermore, treatment with DRB or TBB significantly reduced the frequency of miniature EPSCs of spinal dorsal horn neurons increased by FK506 treatment. In addition, intrathecal injection of DRB or TBB dose-dependently reversed tactile allodynia and mechanical hyperalgesia in FK506-treated rats. Collectively, our findings indicate that CK2 inhibition abrogates pain hypersensitivity and increased pre- and postsynaptic NMDAR activity in the spinal cord caused by calcineurin inhibitors. CK2 inhibitors may represent a new therapeutic option for the treatment of CIPS.

INTRODUCTION

Calcineurin is a Ca²⁺/calmodulin-dependent serine/threonine protein phosphatase, which is present in the T cells of the immune system and in the nervous system, including the dorsal root ganglion and spinal cord (Strack et al., 1996; Wu et al., 2005, 2006). Calcineurin inhibitors, such as tacrolimus (FK506) and cyclosporine A, are commonly used immunosuppressants and have greatly improved the long-term survival of patients after organ and tissue transplantation. However, these drugs can result in unexplained severe pain and pain hypersensitivity, clinically known as calcineurin inhibitor-induced pain syndrome (CIPS) (Grotz et al., 2001; Collini et al., 2006; Noda et al., 2008; Kakihana et al., 2012). CIPS predominantly affects the lower limbs, and the pain is particularly excruciating during standing and walking (Grotz et al., 2001; Fujii et al., 2006; Noda et al., 2008). Because the underlying mechanisms of CIPS are not fully known, effective treatments for CIPS are still limited. We recently developed a rat model of CIPS in which systemic administration of FK506 causes a long-lasting pain hypersensitivity (Chen et al., 2014). We have shown that repeated FK506 treatment in rats increases pre- and postsynaptic N-methyl-D-aspartate receptor (NMDAR) activity in the spinal dorsal horn and that blocking spinal NMDARs can effectively attenuate the pain hypersensitivity caused by FK506 (Chen et al., 2014). Nevertheless, little is known about how spinal NMDAR activity is potentiated by calcineurin inhibitors. Furthermore, because directly blocking NMDARs can produce intolerable side effects in patients, identifying new therapeutic targets involved in NMDAR regulation in CIPS could lead to improved treatment options for patients with CIPS.

NMDAR phosphorylation by the coordinated activities of protein kinases and phosphatases is central to many physiologic functions (Lieberman and Mody, 1994, 1999; Tong...
et al., 1995; MacDonald et al., 1998). Because synaptic NMDARs can fluctuate between phosphorylated and dephosphorylated forms, normal NMDAR function may be controlled by a delicate balance between the activities of protein kinases and protein phosphatases. Calcineurin inhibition may augment NMDAR activity by causing excessive phosphorylation of NMDARs and/or NMDAR-interacting proteins (Tong et al., 1995; Chen et al., 2014). On the other hand, inhibition of protein kinase CK2 (formerly known as casein kinase II) can attenuate NMDAR activity in the brain, possibly by reducing NMDAR phosphorylation (Lieberman and Mody, 1994, 1999; Tong et al., 1995; Ye et al., 2012). CK2 is present in the spinal cord and plays a role in inflammatory pain (Li et al., 2005). We reasoned that if calcineurin and CK2 reciprocally control NMDAR activity through phosphorylation, inhibition of endogenous CK2 might reverse calcineurin inhibitor-induced potentiation of the NMDAR activity in the spinal cord. In the present study, we used a rat model of CIPS to test the hypothesis that CK2 contributes to increased NMDAR activity in the spinal cord and persistent pain hypersensitivity caused by calcineurin inhibitors.

Materials and Methods

Animal Model of CIPS. Eighty-seven adult male Sprague-Dawley rats (280–320 g; Harlan, Indianapolis, IN) were used for the study. The specific calcineurin inhibitor FK506 was used to induce CIPS in the rats, as we previously described (Chen et al., 2014). FK506 (1.5 mg/kg) was dissolved in dimethylsulfoxide (DMSO) and injected intraperitoneally once a day for 7 days. Rats in the control group received daily intraperitoneal injections of the vehicle (DMSO). A series of calibrated von Frey filaments were applied to the paw or vocalizing, and the nociceptive threshold of the animal was measured by a Ugo Basile analgesimeter (Varese, Italy). A noxious pressure stimulus was applied to determine the mechanical nociceptive threshold of the hindpaw, we used a rat model of CIPS to test the hypothesis that FK506 contributes to increased NMDAR activity in the spinal cord and persistent pain hypersensitivity caused by calcineurin inhibitors.

Behavioral Assessments of Mechanical Nociception. To measure tactile hypersensitivity, each animal was placed in an individual plastic box on a mesh floor and allowed to acclimate for 30 minutes. A series of calibrated von Frey filaments were applied perpendicularly to the plantar surface of the hindpaw with sufficient force to bend the filaments for 6 seconds. Brisk paw withdrawal or flinching was considered a positive response. The tactile stimulus producing a 50% likelihood of withdrawal was determined by using the “up-down” method (Chaplan et al., 1994; Chen et al., 2000).

Spinal Cord Slice Preparation and Electrophysiological Recordings. The lumbar segment of the spinal cord at the L4-L6 level was rapidly removed through laminectomy after the rats were anesthetized with the use of 2–3% isoflurane. The spinal cord tissues were immediately placed in ice-cold artificial cerebrospinal fluid containing (in mM) 234 sucrose, 3.6 KCl, 1.2 MgCl2, 2.5 CaCl2, 1.2 NaHPO4, 25.0 NaHCO3, and 12.0 glucose. The spinal cord was glued onto the stage of a vibratome. Transverse spinal cord slices were cut (400 μm in thickness) in ice-cold sucrose artificial cerebrospinal fluid and then incubated in Krebs solution prewarmed with 95% O2 and 5% CO2 at 34°C for at least 1 hour before being transferred to the recording chamber.

The spinal slice was continuously perfused with Krebs solution at 5.0 mL/min at 34°C, and neurons were visualized on a fixed-stage microscope with differential interference contrast/infrared illumination. Lamina II outer zone neurons were selected for electrophysiological recordings because they are the central site of termination for the majority of unmyelinated C-fibers carrying nociceptive information (Cervero and Iggo, 1980; Pan et al., 2003). It has been demonstrated that most neurons in lamina II are glutamate-releasing excitatory interneurons (Santos et al., 2007). Excitatory postsynaptic currents (EPSCs) were recorded using whole-cell voltage-clamp techniques (Pan and Pan, 2004; Pan et al., 2008). The impedance of the glass electrode was 5–10 MΩ when the pipette was filled with the internal solution containing (in mM) 135 potassium gluconate, 5 KCl, 2.0 MgCl2, 0.5 CaCl2, 5.0 HEPES, 5.0 EGTA, 5.0 ATP-Mg, 0.5 Na-GTP, and 10 QX-314 (adjusted to pH 7.25 with 1.0 M Ca(OH2, 280–300 mOsm). EPSCs were evoked from the dorsal root using a bipolar tungsten electrode connected to a stimulator (0.6 mA, 0.2 ms, and 0.1 Hz; Grass Instruments, Quincy, MA). α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-mediated EPSCs (AMPAR-EPSCs) were recorded in the presence of 2 mM strychnine and 10 mM bicuculline. NMDAR-mediated EPSCs (NMDAR-EPSCs) were recorded in the presence of 2 μM strychnine, 10 μM bicuculline, and 20 μM 6-cyano-7-nitroquinoxaline-2,3-dione at a holding potential of +40 mV (Li et al., 2008; Zhou et al., 2012). In addition, miniature EPSCs (mEPSCs) were recorded at a holding potential of −60 mV in the presence of 1 μM tetrodotoxin, 10 μM bicuculline, and 2 μM strychnine. The input resistance was continuously monitored, and the recording was abandoned if the resistance change was more than 15%.

To directly determine postsynaptic NMDAR activity, currents were elicited by puff application of 100 μM NMDA to the recorded neuron in the extracellular solution containing a low concentration of Mg2+ (0.1 mM), 10 μM glycine, and 1 μM tetrodotoxin at a holding potential of −60 mV (Li et al., 2008; Zhou et al., 2012). The pipette internal solution contained (in mM) 110.0 Cs2SO4, 2.0 MgCl2, 0.1 CaCl2, 1.1 EGTA, 10.0 HEPES, 2.0 MgATP, and 0.3 Na2GTP (pH was adjusted to 7.25 with 1.0 M Ca(OH2, 280–300 mOsm) (Li et al., 2008; Zhou et al., 2012). The puff electrode was placed approximately 150 μm away from the recorded neuron in the extracellular solution containing a low concentration of Mg2+ (0.1 mM), 10 μM glycine, and 1 μM tetrodotoxin at a holding potential of −60 mV (Li et al., 2008; Zhou et al., 2012).

Statistical Analysis. All the data are expressed as means ± S.E.M. To determine the amplitude of the evoked EPSCs, 6–10 consecutive EPSCs were averaged and analyzed offline with Clampfit 9.2.
software (Axon Instruments). The mEPSCs were analyzed offline with a peak detection program (MiniAnalysis, Synaptosoft Inc., Decatur, GA). For the statistical analysis of electrophysiological data, one-way analysis of variance followed by Dunnett's or Tukey's post hoc test was used. The effects of CK2 inhibitors on the paw withdrawal thresholds were determined by one-way analysis of variance followed by Dunnett's post hoc test. A P value of < 0.05 was considered statistically significant.

Results

CK2 Contributes to Potentiated Synaptic NMDAR Currents of Spinal Dorsal Horn Neurons in FK506-Treated Rats. To determine the contribution of CK2 to increased synaptic NMDAR activity of spinal dorsal horn neurons in FK506-treated rats, we used two selective and structurally dissimilar CK2 inhibitors, DRB (100 μM) and TBB (2 μM), which competitively inhibit the binding of the phosphate donors ATP and GTP to CK2 (Sarno et al., 2001, 2002). It is noteworthy that DRB is a highly specific CK2 inhibitor, and it does not affect protein kinase C, protein kinase A, calmodulin-dependent protein kinase II, or the Src tyrosine kinase (Pinna, 1990). The concentrations of DRB and TBB selected for our study have been shown to inhibit CK2 activity in rat brain slices (Lieberman and Mody, 1999; Ye et al., 2011). We recorded AMPAR-EPSCs and NMDAR-EPSCs of lamina II neurons monosynaptically evoked from dorsal root stimulation in spinal cord slices obtained from vehicle-treated and FK506-treated rats. Monosynaptic EPSCs were identified on the basis of the constant latency of evoked EPSCs and the absence of conduction failure of evoked EPSCs in response to a brief 20-Hz electrical stimulation (Li et al., 2002; Zhou et al., 2010).

Although the amplitude of evoked AMPAR-EPSCs of spinal dorsal horn neurons did not differ significantly between vehicle-treated control rats (n = 11 neurons) and FK506-treated rats (n = 10 neurons), the amplitude of NMDAR-EPSCs was much larger in FK506-treated rats than in vehicle-treated rats (115.71 ± 6.86 versus 40.02 ± 4.17 pA, P < 0.05; Fig. 1, A and B). Furthermore, the ratio of NMDAR-EPSCs to AMPAR-EPSCs in these neurons was significantly greater in FK506-treated rats than in vehicle-treated rats (Fig. 1C). Treatment of spinal cord slices with either 100 μM DRB (n = 11 neurons) or 2 μM TBB (n = 10 neurons) for approximately 2 hours completely normalized the amplitude of evoked NMDAR-EPSCs and the ratio of NMDAR-EPSCs to AMPAR-EPSCs in FK506-treated rats (Fig. 1, A–C).

CK2 Inhibition Normalizes Postsynaptic NMDAR Currents of Spinal Dorsal Horn Neurons in FK506-Treated Rats. To directly determine whether CK2 plays a role in increased postsynaptic NMDAR activity in the spinal cord of FK506-treated rats, we determined the effect of DRB or TBB on NMDAR currents induced by puff application of 100 μM NMDA to the recorded lamina II neurons of FK506-treated rats. The amplitude of puff NMDA-elicited NMDAR currents of lamina II neurons in FK506-treated rats (n = 13 neurons) was significantly larger than that in vehicle-treated control rats (n = 13 neurons) (Fig. 2, A and B). Treatment of spinal cord slices from FK506-treated rats with DRB (100 μM, n = 13 neurons) or TBB (2 μM, n = 11 neurons) for approximately 2 hours profoundly decreased the amplitude of puff NMDAR currents of lamina II neurons (Fig. 2, A and B).

Fig. 1. CK2 inhibition normalizes synaptic NMDAR activity in the spinal dorsal horn increased by FK506 treatment. (A) Original current traces (averaged responses from 6 EPSCs) show that NMDAR-EPSCs (at the holding potential of +40 mV) and AMPAR-EPSCs (at the holding potential of −60 mV) recorded from lamina II neurons potentiated by FK506 treatment. *P < 0.05 compared with the value in the vehicle control group.
Control rats (Fig. 3, A). Representative traces show NMDAR currents elicited by puff application of 100 μM NMDA to the lamina II neuron in spinal cord slices obtained from one control rat, one rat treated with systemic injection of FK506, one FK506-treated rat plus DRB treatment (100 μM for ~2 hours), and one FK506-treated rat plus TBB treatment (2 μM for ~2 hours). (B) Group data show the effect of DRB and TBB on the amplitude of puff NMDA-elicited NMDAR currents of lamina II neurons. *P < 0.05 compared with the value in the vehicle-treated control group.

Fig. 2. CK2 Inhibition reduces postsynaptic NMDAR currents of spinal dorsal horn neurons potentiated by FK506 treatment. (A) Representative traces show NMDAR currents elicited by puff application of 100 μM NMDA to the lamina II neuron in spinal cord slices obtained from one control rat, one rat treated with systemic injection of FK506, one FK506-treated rat plus DRB treatment (100 μM for ~2 hours), and one FK506-treated rat plus TBB treatment (2 μM for ~2 hours). (B) Group data show the effect of DRB and TBB on the amplitude of puff NMDA-elicited NMDAR currents of lamina II neurons. *P < 0.05 compared with the value in the vehicle-treated control group.

In fact, DRB or TBB treatment normalized the amplitude of puff NMDAR currents of FK506-treated rats to that of control rats. These data suggest that CK2 contributes to the increased postsynaptic NMDAR activity of spinal dorsal horn neurons induced by the calcineurin inhibitor.

CK2 Is Involved in Increased Presynaptic NMDAR Activity of Spinal Dorsal Horn Neurons in FK506-Treated Rats. Presynaptic NMDARs regulate synaptic glutamate release in the spinal cord (Zhao et al., 2012). Systemic treatment with FK506 increases synaptic glutamate release through stimulation of presynaptic NMDARs in the spinal cord (Chen et al., 2014). To determine whether CK2 plays a role in FK506 treatment-induced increases in presynaptic NMDAR activity in the spinal cord, we tested the effect of DRB and TBB on glutamatergic mEPSCs (reflecting presynaptic quantal release of glutamate) of lamina II neurons in FK506-treated rats. The baseline frequency (4.85 ± 0.55 versus 3.34 ± 0.47 Hz, P < 0.05), but not the amplitude, of mEPSCs in lamina II neurons of FK506-treated rats (n = 15 neurons) was significantly higher than that in control rats (n = 16 neurons) (Fig. 3, A–D). Furthermore, bath application of the specific NMDAR antagonist AP5 (50 μM) significantly reduced the frequency of mEPSCs in FK506-treated rats but not in control rats (Fig. 3, A–D).

Treatment of spinal cord slices from FK506-treated rats with DRB (100 μM, n = 19 neurons) or TBB (2 μM, n = 18 neurons) for approximately 2 hours significantly reduced the baseline frequency of mEPSCs in lamina II neurons, but it had no significant effect on the amplitude of mEPSCs (Fig. 4, A–C). The baseline frequency of mEPSCs in lamina II neurons in DRB- or TBB-treated spinal cord slices in FK506-treated rats was similar to that in control rats. In addition, bath application of AP5 (50 μM) had no significant effect on the frequency of mEPSCs in FK506-treated rats after treatment with DRB or TBB (Fig. 4, A–C). These results suggest that CK2 contributes to the increased presynaptic NMDAR activity and synaptic glutamate release to spinal dorsal horn neurons caused by calcineurin inhibitors.

Discussion

Calcineurin inhibitors can cause pain and pain hypersensitivity in patients receiving organ and tissue transplants (Grotz et al., 2001; Fujii et al., 2006; Noda et al., 2008; Kakihana et al., 2012). The primary treatment of CIPS is discontinuation of these agents, which could endanger the transplanted organs and tissues. We demonstrated recently that systemic administration of FK506 can lead to unrestrained nociceptive input by potentiating NMDARs at the spinal cord level (Chen et al., 2014). NMDAR activity and phosphorylation state are dynamically controlled by a balance between the activity of protein kinases and protein phosphatases. For example, CK2 activation increases the phosphorylation and activity of NMDARs, whereas calcineurin can negatively regulate the phosphorylation and function of NMDARs in the brain (Tong et al., 1995; Lieberman and Mody, 1999; Ye et al., 2011). CK2 is an endogenous serine/threonine protein kinase widely expressed in many types of cells and is distributed in the central nervous system (Blanquet, 2000; Litchfield, 2003). CK2 is specifically distributed in postsynaptic densities,
which are crucial for modulating synaptic NMDAR function (Chung et al., 2004; Soto et al., 2004). Although the mechanisms responsible for increased spinal NMDAR activity by calcineurin inhibitors are not fully known, it is possible that in CIPS the phosphorylation/dephosphorylation cycle of NMDARs in the spinal dorsal horn is shifted to a predominantly phosphorylated state through reduced calcineurin activity.

In this study, we used whole-cell patch-clamp recordings of glutamatergic EPSCs in spinal cord slices to determine...
whether inhibition of CK2 can lead to a “rebalancing” of spinal NMDAR activity potentiated by a calcineurin inhibitor. We observed that blocking NMDARs with AP5 significantly reduced the basal frequency of mEPSCs only in FK506-treated rats. These results suggest that presynaptic NMDAR activity is augmented by calcineurin inhibition, resulting in increased synaptic glutamate release to spinal dorsal horn neurons. It is noteworthy that we found that treatment of spinal cord slices with either of two structurally distinct CK2 inhibitors, DRB and TBB, significantly reduced the baseline frequency of mEPSCs of dorsal horn neurons in FK506-treated rats. Furthermore, AP5 no longer had any effect on the frequency of mEPSCs in dorsal horn neurons of FK506-treated rats after treatment with DRB or TBB. Our data indicate that CK2 inhibition normalizes synaptic glutamate release to spinal dorsal horn neurons by reducing presynaptic NMDAR activity potentiated by the calcineurin inhibitor.

Increased postsynaptic NMDAR activity in the spinal dorsal horn by a calcineurin inhibitor may facilitate nociceptive transmission by amplifying excitatory input from primary sensory nerves and by diminishing synaptic GABA/glycine inhibition (Leem et al., 1996; Chen et al., 2000; Zhou et al., 2012). We found
that inhibiting CK2 with DRB or TBB completely normalized the amplitude of evoked NMDAR-EPSCs and the ratio of evoked NMDAR-EPSCs to AMPAR-EPSCs in spinal dorsal horn neurons increased by FK506 treatment. On the other hand, neither DRB nor TBB had any significant effects on the amplitude of evoked AMPAR-EPSCs in spinal dorsal horn neurons of FK506-treated rats. Furthermore, DRB or TBB significantly inhibited NMDAR currents of dorsal horn neurons elicited by direct NMDA puff application in FK506-treated rats. Our results strongly suggest that CK2 inhibition normalizes the increased postsynaptic NMDAR activity in the spinal dorsal horn caused by the calcineurin inhibitor. Our findings support the notion that spinal NMDAR activity potentiated by the calcineurin inhibitor probably results from an imbalance between the activity of CK2 and calcineurin. The increased presynaptic and postsynaptic NMDAR activity in the spinal dorsal horn caused by calcineurin inhibition can cause long-lasting tactile allodynia and mechanical hyperalgesia (Chen et al., 2014). To determine whether CK2 inhibition at the spinal cord level can reduce pain hypersensitivity in our rat model of CIPS, we tested the effect of intrathecal injection of CK2 inhibitors on the mechanical hypersensitivity of FK506-treated rats. We found that intrathecal injection of DRB or TBB produced dose-dependent and long-lasting reductions in tactile allodynia and mechanical hyperalgesia induced by systemic FK506 administration in rats. These data indicate that inhibition of CK2 at the spinal level effectively reduces calcineurin inhibitor-induced pain hypersensitivity.

It is not clear how CK2 inhibition normalizes spinal NMDAR activity potentiated by calcineurin inhibition. Our study suggests that the imbalance between the levels of CK2 and calcineurin activity could play a critical role in increased spinal NMDAR activity and pain hypersensitivity induced by calcineurin inhibitors. It is possible that CK2 inhibition may reduce the increased phosphorylation levels of NMDARs and/or NMDAR-interacting proteins brought about by the calcineurin inhibitor. It has been reported that CK2 may increase NMDAR activity through the phosphorylation of the NR2B subunit (Chung et al., 2004) or through indirect mechanisms, possibly involving the NMDAR scaffolding proteins, such as postsynaptic density-95/synapse-associated 90 (Soto et al., 2004). In addition, calmodulin can inhibit NMDAR activity through binding to the NR1 subunit in a Ca$^{2+}$-dependent manner (Ehlers et al., 1996; Krupp et al., 1999). Thus, CK2 inhibition may reduce the phosphorylation level of calmodulin (Sacks et al., 1992), resulting in the inhibition of NMDAR activity by promoting calmodulin binding to the NR1 subunit. Nevertheless, the precise mechanisms through which calcineurin and CK2 interact to alter the phosphorylation of NMDARs and/or their interacting proteins remain unclear and need to be delineated in future studies.

In summary, our study provides important new information that CK2 critically contributes to pain hypersensitivity and increased pre- and postsynaptic NMDAR activity in the spinal dorsal horn caused by calcineurin inhibitors. This new information advances our understanding of the reciprocal relationship between CK2 and calcineurin in the regulation of NMDARs and nociceptive transmission at the spinal cord level. Because directly blocking NMDARs can cause serious side effects in patients (Zhou et al., 2011), NMDAR antagonists may have limited clinical use. CK2 inhibitors, such as CX-4945, have been recently developed for clinical use and...
Fig. 6. Intrathecal injection of TBB attenuates mechanical hypersensitivity of rats induced by systemic administration of FK506. (A) Time course of the effect of intrathecal injection of 100–500 ng of TBB on the paw withdrawal threshold measured with von Frey filaments in rats treated with FK506 (1.5 mg/kg per day for 7 days). (B) Time course of the effect of intrathecal injection of 100–500 ng of TBB on the paw withdrawal threshold measured with a pressure stimulus in rats treated with FK506. *P < 0.05 compared with the respective baseline value (time 0).

A

B

References


Chen SR, Eisenach JC, McCaslin PP, and Pan HL (2000) Synergistic effect between spinal C-fibers and calcineurin inhibitor-induced immunosuppression. Because Ck2 inhibition can also reduce nephrotoxicity induced by calcineurin inhibitors (Son et al., 2013), Ck2 inhibitors may provide additional benefits for treating various side effects produced by calcineurin inhibitors.

Authorship Contributions

Participated in research design: Pan.


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