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BRIEF REPORT

Increased phosphorylation of Ser473-Akt, Ser9-GSK-3β and Ser133-CREB in the rat frontal cortex after MK-801 intraperitoneal injection

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Abstract

GSK-3β is regarded as playing an important part in the pathogenesis of schizophrenia and the action of psychotomimetic agents. We observed phosphorylation of molecules associated with the GSK-3β signalling pathway in the rat brain after MK-801 injection, which induces a schizophrenia-like state in humans. Ser9-GSK-3β phosphorylation was increased after injection of 1 mg/kg MK-801 in the rat frontal cortex but not in the hippocampus or cerebellum. This increase peaked at 30 min and was maintained until 90 min after injection. The phosphorylation showed a dose-dependent increase up to 1 mg/kg MK-801, followed by a decrease at higher dosage. Furthermore, phosphorylation of Ser473-Akt and Ser133-CREB showed similar temporal, dose-dependent and regionally specific patterns with those of Ser9-GSK-3β. However, phosphorylation of Dvl and Ser33-β-catenin was not affected by MK-801. These results suggest that GSK-3β phosphorylation by MK-801 may be associated with the Akt-GSK-3β pathway rather than with the Wnt-Dvl-GSK3β pathway.

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Introduction

Investigations into GSK-3β have focused on its roles in intracellular signalling pathways, which regulate energy metabolism, cellular structure maintenance and regulation of gene transcription (Grimes and Jope, 2001). While the dysfunction of GSK-3β has been suggested in various medical disorders, GSK-3β inhibitors are currently under investigations for their therapeutic potential (Woodgett, 2003).

Dysfunction of GSK-3β has been suggested to be related to psychiatric disorders such as schizophrenia, bipolar disorder and Alzheimer's disease (Beasley et al., 2001; Grimes and Jope, 2001; Kozlovsky et al., 2000; Nadri et al., 2003). The reduction in the protein levels and Ser9 phosphorylation status of GSK-3β have been reported in the post-mortem frontal cortex of schizophrenic patients (Emamian et al., 2004). In the frontal cortex of rats with neonatal ventral hippocampal lesion used as a model of schizophrenia, the level of GSK-3β was also reduced (Nadri et al., 2003). GSK-3β has been considered as a molecular target of mood stabilizers such as lithium and valproate (Chen et al., 1999; Grimes and Jope, 2001), and its phosphorylation is also affected by clozapine and ECS, which are well known treatment modalities for schizophrenia and bipolar disorder (Kang et al., 2004; Roh et al., 2003).

GSK-3β can be phosphorylated either by Akt or the canonical Wnt signal. Both Akt and the Wnt signal have been implicated in GSK-3β phosphorylation by antipsychotics. Acute haloperidol treatment has been reported to increase the phosphorylation of Thr308-Akt and Ser9-GSK-3β, while chronic haloperidol increases both Thr308 and Ser473-Akt which leads to the increased phosphorylation of Ser9-GSK-3β. The same study also reported decreased levels of Akt1

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protein and the phosphorylation of Ser9-GSK-3β in the peripheral lymphocytes and brains of schizophrenics (Emamian et al., 2004). We, on the other hand, previously reported that clozapine increased the phosphorylation of Ser9-GSK-3β via the Wnt pathway, rather than via the PI3K-Akt signalling pathway (Kang et al., 2004).

Recently, the psychotomimetics used in animal schizophrenic models have also been shown to phosphorylate GSK-3β. In the mouse frontal cortex, the increased phosphorylation of Ser9-GSK-3β, along with that of Thr34-DARPP-32, Ser130-DARPP-32 and Ser133-CREB, has been reported after treatment of psychotomimetic drugs, such as d-amphetamine, lysergic acid diethylamide (LSD) and phencyclidine (PCP). However, these changes were not observed in the hippocampus or cerebellum. Hence, phosphorylation of GSK-3β appears to be a common pathway through which diverse psychotomimetic drugs show effect (Svenningsson et al., 2003).

The non-competitive NMDA receptor antagonist MK-801 has psychotomimetic effects closely resembling the symptoms of schizophrenia (Javitt and Zukin, 1991; Olney and Farber, 1995). Although Svenningsson et al. (2003) did not directly present results for MK-801, they commented that MK-801 seems to act through a mechanism similar to PCP in the phosphorylation of DARPP-32 in the mouse brain. Therefore, the phosphorylation of GSK-3β may be increased by MK-801 injection. However, there is a report that MK-801 reduces p-Akt levels upstream of GSK-3β in cortical neuronal cultures (Sutton and Chandler, 2002). Therefore, the result reported by Sutton and Chandler is not consistent with the assumption based on the comment of Svenningsson et al. (2003). This controversy also encompasses the phosphorylation of CREB. Although Svenningsson et al. (2003) reported that many psychotomimetics, including PCP, increase the phosphorylation of CREB, MK-801 was known to reduce p-CREB levels in primary striatal cultures (Dudman et al., 2003).

In this paper, we first examined whether MK-801 injection increases the phosphorylation of Ser9-GSK-3β in the rat brain with regional specificity and in a dose-dependent manner. Second, we investigated whether the upstream mechanism of Ser9-GSK-3β phosphorylation is the canonical Wnt pathway and/or the Akt pathway. Third, between the two sites phosphorylated in Akt, Ser473 and Thr308, we determined which site was involved in MK-801. Finally, we observed whether the phosphorylation of Ser133-CREB, after MK-801 injection, shows similar temporal and regional patterns with that of Ser9-GSK-3β.

Materials and methods

Animals and drug treatment

Male Sprague–Dawley rats (150–200 g) were grouped and maintained on a 12 h, light/dark cycle with food and water freely available. Animals were treated in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

MK-801 (Tocris, Ellisville, MO, USA), dissolved in normal saline, was injected into the rats intraperitoneally and control animals received an equivalent volume of normal saline. According to our previous observation, the level of c-Fos definitely increased in the cerebral cortex from administration of 0.25 mg/kg MK-801, peaked with 1–2 mg/kg, and then decreased (Ahn et al., 2002). In terms of behavioural activation, there is a report of maximal behavioural activation after injection of 1 mg/kg MK-801 in locomotion and stereotyped sniffing (Andine et al., 1999), which is in agreement with the results of our previous study (Ahn et al., 2002). Therefore, we chose 1 mg/kg as the dose to determine the temporal profile. To examine the relation between MK-801 dosage and phosphorylation, we observed the level of phosphorylation at 60 min after MK-801 injection because preliminary results showed no changes in the phosphorylation after 60 min at each dose. Furthermore, there is a report that MK-801-induced locomotion, stereotyped sniffing and ataxia are fully and stably developed around 60 min after MK-801 injection (Andine et al., 1999).

Western blot analysis

The brain was dissected on an ice plate. The hippocampus and frontal cortex were immediately homogenized in 10 vol (v/w) of pre-chilled buffer containing 25 mM Hepes (pH 7.9), 200 mM NaCl, 1.5 mM $MgCl_2$, 0.2% NP-40, 1 mM DTT, 0.5 mM EDTA, 1 mM PMSF, 20 mM β-glycerophosphate, 2 mM NaF, 0.1 mM Na_3VO_4 and 2 mg/l leupeptin. Homogenates were centrifuged and the supernatants were boiled with Laemmli sample buffer. Samples were fractionated in 8% SDS–PAGE gel and then transferred to nitrocellulose membranes (Schleicher & Schuell Bioscience, Dassel, Germany). The membranes were then incubated with Ser9-GSK-3β, Ser133-CREB, Ser473-Akt, Thr308-Akt (Cell Signaling Technology, Beverly, MA, USA), Ser33-β-catenin and dishevelled (Dvl) (Santa Cruz Biotechnology, Santa Cruz, CA, USA) specific antibody at a dilution of 1:1000 overnight at 4 °C. The membranes were then incubated with the anti-rabbit IgG conjugated to horseradish peroxidase (Santa Cruz Biotechnology) and the signal

was detected with the ECL system (Pierce, Rockford, IL, USA). The duration of film exposure was adjusted according to the preliminary experiments.

Results

In the rat frontal cortex, after injection of 1 mg/kg MK-801, the phosphorylation of Ser9-GSK-3β was increased from 15 min compared to the control, peaked at 30 min and was maintained until 90 min after injection of MK-801. The phosphorylation of both Ser473-Akt and Ser133-CREB, upstream and downstream molecules of GSK-3β respectively, followed the same temporal course after injection of 1 mg/kg MK-801. However, the phosphorylation of Thr308-Akt was not changed (Figure 1).

We examined the effect of each dose of MK-801 at 60 min after injection in the rat frontal cortex. The phosphorylation of Ser9-GSK-3β showed a dose-dependent increase up to 1 mg/kg MK-801, followed by a decrease at higher dosage. Interestingly, at 8 mg/kg, a dose which clearly elicited no movement in the rats, the level of phosphorylation was below that of the control. The phosphorylation of Ser473-Akt and Ser133-CREB showed parallel, dose-dependent patterns with the phosphorylation of Ser9-GSK-3β (Figure 2).

To clarify the upstream mechanism of Ser9-GSK-3β phosphorylation, we also examined the mobility shift of Dvl, as the phosphorylation of Dvl is involved with GSK-3β phosphorylation in the canonical Wnt pathway. However, we did not observe any change in the mobility shift of Dvl. In addition, we also examined the level of Ser33-β-catenin phosphorylation and the amount of β-catenin, another downstream molecule of Ser9-GSK-3β, in the canonical Wnt pathway, but there was no change in the phosphorylation or amount of β-catenin (Figure 3).

In contrast to the rat frontal cortex, we observed no increase in the phosphorylation of Ser9-GSK-3β, Ser473-Akt and Ser133-CREB in the rat hippocampus and cerebellum (data not shown).

Discussion

We observed that MK-801 increased the phosphorylation of Ser9-GSK-3β in the rat brain with regional specificity and characteristic dose-dependent pattern. Also we observed that the phosphorylation of Ser473-Akt and Ser133-CREB showed the same regional specificity and similar temporal and dose-dependent patterns as those of the phosphorylation of Ser9-GSK-3β. The similarity of these patterns suggests that the

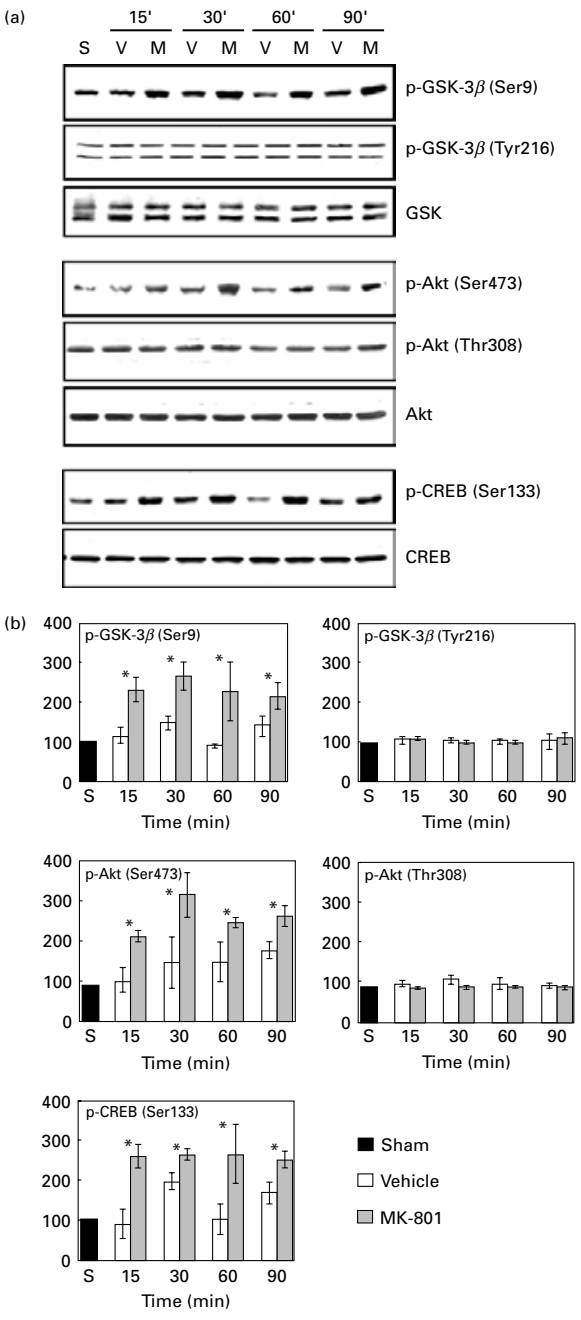

Figure 1. The phosphorylation of GSK-3β, Akt and CREB in the rat frontal cortex. (a) Immunoblots of rat frontal cortex after exposure to MK-801 (1 mg/kg) for the indicated periods. The phosphorylation of Ser9-GSK-3β, Ser473-Akt and Ser133-CREB was increased from 15 min, peaked at 30 min and was maintained until 90 min. (b) Quantification of immunoblot data by densitometric analysis of band intensity. Data are expressed as optical density and represent means $\pm$ S.E.M. of three independent experiments. OD (optical densities) ratio = (OD of the phosphorylation bands of the MK-801-injected group)/(OD of the phosphorylation bands of the vehicle-injected group). Asterisks (*) indicate significant difference ($p < 0.05$, Wilcoxon signed rank test).

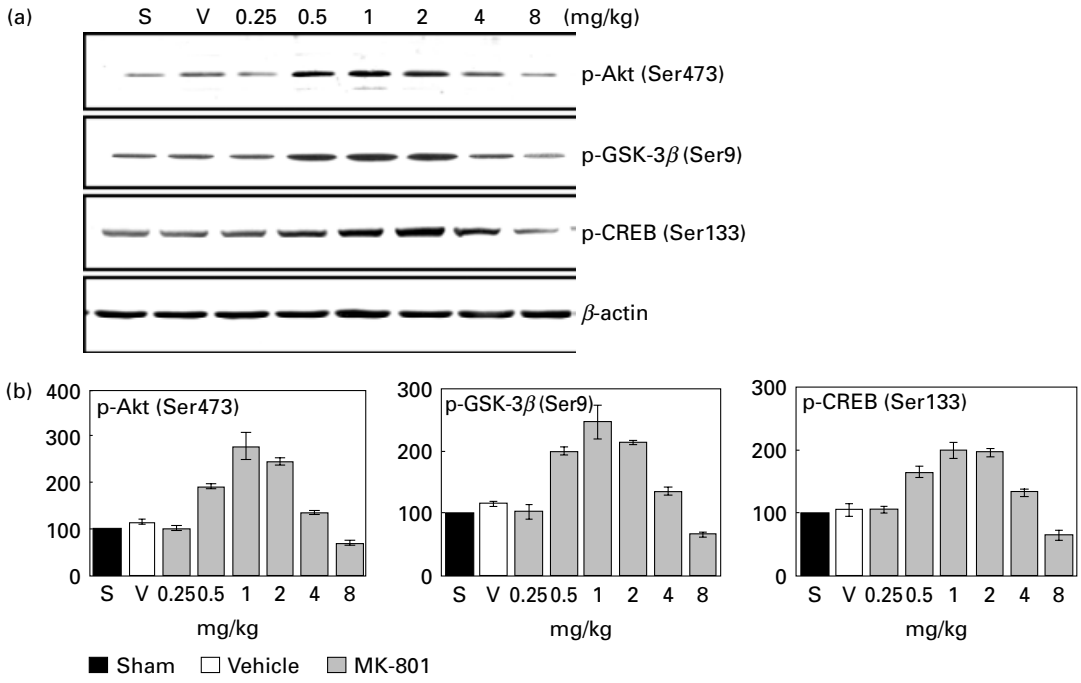

Figure 2. MK-801 dose-dependent patterns of the phosphorylation of GSK-3β, Akt and CREB in the rat frontal cortex. (a) Immunoblots of the rat frontal cortex at 60 min after exposure to MK-801 for the indicated doses. The phosphorylation of Ser9-GSK-3β, Ser473-Akt and Ser133-CREB was increased up to 1 mg/kg, and then decreased. (b) Quantification of immunoblot data by densitometric analysis of band intensity. Data are expressed as optical density and represent means $\pm$ S.E.M. of three independent experiments.

phosphorylation of Ser9-GSK-3β may be correlated with that of Ser473-Akt and Ser133-CREB. Therefore, the Akt signalling pathway may act as an upstream mechanism of Ser9-GSK-3β phosphorylation induced by MK-801.

To enhance the understanding of psychoses and their treatment, it is very important to determine the common pathway which is involved in the pathophysiology of psychoses and the mechanism of psychotomimetics. In a previous study by Svenningsson et al. (2003), the increased phosphorylation of Ser9-GSK-3β and Ser133-CREB in the rat frontal cortex was claimed as one of the common signalling pathways along which diverse psychotomimetics act. We directly showed that another psychotomimetic, MK-801, also induced similar results to those of Svenningsson et al. (2003) in terms of the phosphorylation of Ser9-GSK-3β and Ser133-CREB. Furthermore, our observation of the regional specific pattern of phosphorylation is the same as that of Svenningsson et al. (2003).

Although the Akt-GSK-3β signalling pathway was suggested as a critical signalling pathway for the pathogenesis of schizophrenia and the action of antipsychotics (Emamian et al., 2004), the relationship between the signalling pathway of GSK-3β and the action of psychotomimetics remains to be elucidated. To clarify the upstream mechanism of Ser9-GSK-3β phosphorylation, we examined the phosphorylation of Ser473-Akt and the mobility shift of Dvl. The phosphorylation of GSK-3β can be affected by either the canonical Wnt or Akt pathway. In the canonical Wnt pathway, the binding of Wnt to the Frizzled protein increases the phosphorylation of the adaptor protein Dvl, which leads to the phosphorylation deactivation of GSK-3β. Through this deactivation, the phosphorylation status of β-catenin is decreased, which releases β-catenin from the complex of Axin, APC and β-catenin, and the released β-catenin enters into the nucleus (Aoki et al., 1999). In the Akt pathway, signalling events leading to the activation of Akt can phosphorylate and thereby regulate many signal molecules including GSK-3β (Kandel and Hay, 1999). Ser133-CREB is reported as downstream of the Akt pathway (Du and Montminy, 1998) and also as a substrate for GSK-3β (Grimes and Jope, 2001; Salas et al., 2003), although its phosphorylation is activated by several kinases other than GSK-3β (Lonze and Ginty, 2002). We observed that the phosphorylation of Ser473-Akt and Ser133-CREB, showed the same regional specificity and similar temporal and

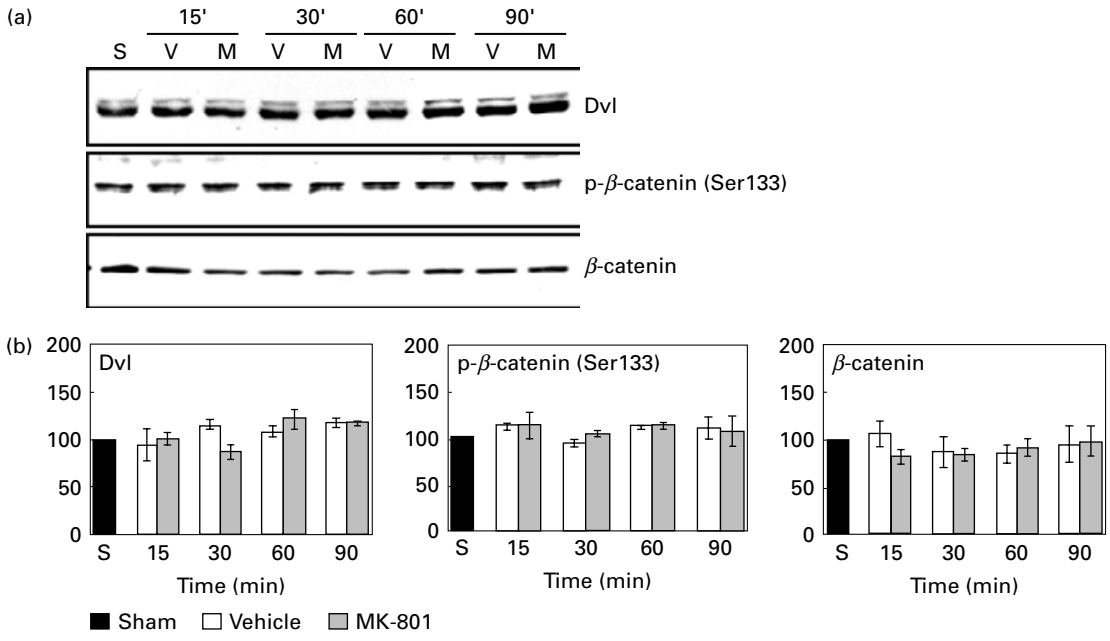

Figure 3. Dvl mobility shift assay, and the amount and phosphorylation of β-catenin in the rat frontal cortex. (a) There was no mobility shift of Dvl and immunoblots showed that there was no change in the phosphorylation or amount of Dvl and β-catenin. (b) Quantification of immunoblot data by densitometric analysis of band intensity. Data are expressed as optical density and represent means ± S.E.M. of three independent experiments.

dose-dependent patterns as Ser9-GSK-3β. However, the phosphorylation of Dvl and Ser33-β-catenin, which are representative upstream and downstream signal transduction molecules respectively, of GSK-3β in the canonical Wnt pathway, were not changed by MK-801 injection. Therefore, the canonical Wnt pathway does not seem to act upstream of the MK-801-induced Ser9-GSK-3β phosphorylation in our experimental conditions. Our results suggest that the Akt-GSK-3β pathway, rather than the canonical Wnt pathway, may play an important role as one of the signalling pathways for MK-801.

Akt has several phosphorylation sites. Among them, the phosphorylation of Thr308 by PDK1 (phosphoinositide-dependent kinase 1) and the phosphorylation of Ser473 by autophosphorylation and by uncharacterized kinases is important in Akt regulation (Alessi and Cohen, 1998; Scheid and Woodgett, 2003; Sutton and Chandler, 2002; Toker and Newton, 2000). Therefore, we examined the changes in Thr308 and Ser473-Akt phosphorylation after MK-801 intraperitoneal injection and found that only the phosphorylation of Ser473-Akt was affected by MK-801 in the rat frontal cortex. Interestingly, Kitagawa et al. (2002) reported that the exposure of cultured neurons to glutamate in rats induced the phosphorylation of Ser473-Akt and Ser133-CREB but showed no change in Thr308-Akt phosphorylation and no enhancement in Akt kinase activity. Although MK-801 is an NMDA receptor antagonist, these findings are quite similar to our observations of increased phosphorylation of Ser473-Akt and Ser133-CREB, but no change in Thr308-Akt phosphorylation, after injection of <8 mg/kg MK-801 in the rat frontal cortex. However, Sutton and Chandler (2002) reported that MK-801 (10 μM) treatment in cortical neuronal culture reduces the phosphorylation of Ser473-Akt compared to basal levels. According to our previous study, 8 mg/kg MK-801 pretreatment completely blocked ECS-induced seizure and partially blocked the induction of c-Fos (Ahn et al., 2002). In this report, a 8 mg/kg MK-801 injection also reduced the phosphorylation of Ser473-Akt, Ser9-GSK-3β and Ser133-CREB in the rat frontal cortex. This suggests that the MK-801 dosage is important in determining the phosphorylation of the Akt-GSK-3β signalling pathway.

Our finding that MK-801, an NMDA receptor antagonist, increases the phosphorylation of Ser473-Akt seems to contradict a previous report that the activation of the NMDA receptor increases the phosphorylation of Ser473-Akt (Kitagawa et al., 2002). However, Sutton and Chandler (2002) reported that the NMDA dose–response curve for the stimulation of phospho-PKB(Akt) is biphasic. Furthermore, the

possibility that MK-801 may activate Ser473-Akt through a mechanism independent of the NMDA receptor cannot be excluded (Olney and Farber, 1995). Taken together with our finding that MK-801 increases the phosphorylation of Ser473-Akt, this result cannot be explained by a simple linear relation between NMDA receptor activity and Akt phosphorylation.

According to our observations, the phosphorylation of Ser9-GSK-3β, Ser473-Akt and Ser133-CREB, after injection of 1 mg/kg MK-801, was increased from 15 min, peaked at 30 min and was maintained until 90 min. This temporal pattern is basically correlated with the temporal profile of behavioural changes that are observed in a rat model of psychosis induced by the psychotomimetic, MK-801. It was reported that the first sign of locomotion and stereotyped sniffing in rats was observed at 20–25 min after MK-801 administration (0.2 mg/kg i.p., 60 d old; Andine et al., 1999). Meanwhile, according to the dose-dependent pattern in the present study, the phosphorylation peaked at 1 mg/kg. This finding also basically correlates with the same report by Andine et al. (1999) that the rat showed maximal behavioural activation in locomotion and stereotyped sniffing after 1 mg/kg MK-801, whereas with 3 mg/kg it merely showed extensive ataxia without locomotion. Therefore, these findings suggest that the changes in the phosphorylation may reflect the behavioural changes induced by MK-801, which demonstrates the importance of the phosphorylation of Ser9-GSK-3β in the biochemical mechanism of MK-801 as a psychotomimetic.

Taken together, our observations suggest that the phosphorylation of Ser473-Akt, Ser9-GSK-3β and Ser133-CREB may play an important role in the mechanism of MK-801 as a psychotomimetic agent.

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Statement of Interest

None.

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