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Research Paper

Evidence of the involvement of K^+ channels and PPARγ receptors in the antidepressant-like activity of diphenyl diselenide in mice

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Abstract

Objectives This study investigated the involvement of different types of K^+ channels and PPARγ receptors in the antidepressant-like effect of diphenyl diselenide in mice.

Methods Mice were pretreated with subeffective doses of K^+ channel inhibitors (tetraethylammonium, glibenclamide, charybdotoxin and apamin), openers (cromakalim, minoxidil), GW 9662 (a PPARγ antagonist) or vehicle. Thirty minutes later the mice received diphenyl diselenide in either an effective or a subeffective dose, 30 min before a tail-suspension test.

Key findings Pre-treatment with tetraethylammonium, charybdotoxin or apamin combined with a subeffective dose of diphenyl diselenide was effective in decreasing the immobility time in the mouse tail-suspension test. The reduction in the immobility time elicited by an effective dose of diphenyl diselenide in this test was prevented by the pretreatment of mice with minoxidil and GW 9662.

Conclusions Diphenyl diselenide elicited an antidepressant-like effect and this action was mediated, at least in part, by modulation of K^+ channels and PPARγ receptors.

Keywords antidepressant; peroxisome proliferator-activated receptor gamma; potassium channels; selenium

Introduction

Depression is a chronic mental disorder, clinically characterised by a pervasive low mood, loss of interest or pleasure in daily activities, low self-esteem and a high suicidal tendency.[1] Conventional available antidepressants are inadequate for many individuals and have frequent and persistent side effects. For these reasons, the discovery of new drugs or innovative compounds that could further improve current depression therapies are welcomed.[2]

Diphenyl diselenide $(PhSe)_2$, an organoselenium compound, exerts biological actions, including antioxidant,[3] hepatoprotective,[4] hypolipidaemic,[5] anti-ulcer,[6] anti-inflammatory, antinociceptive and antidepressant-like effects.[7,8] Although $(PhSe)_2$ has several pharmacological properties, there have been no preclinical studies with this molecule.

Studies in humans have demonstrated the role of selenium in mood disorders.[9,10] Low selenium levels (a low-selenium diet contains 32–36 μg per day) have been associated with a significant increased incidence of depression, anxiety, confusion and hostility. In addition, high dietary and/or supplementary selenium (226 μg per day) improves mood.[11]

In this context, $(PhSe)_2$ is an attractive possibility for the treatment of depression, as it exerts antidepressant-like and anxiolytic-like effects.[7,12] In addition, the antidepressant-like effect of $(PhSe)_2$ is mediated, at least in part, by an interaction with the L-arginine-nitric oxide (NO)-soluble guanylate cyclase (sGC) pathway and may be related to serotonergic, noradrenergic and dopaminergic mechanisms.[7,12] However, additional mechanisms of action that might be involved in the antidepressant-like effect of $(PhSe)_2$ still need further investigation.

It has been reported that NO can activate different types of K^+ channels in smooth muscle and brain.[13,14] The involvement of K^+ channels in the modulation of depression has been suggested by several preclinical studies. Different types of K^+ channel inhibitors, such as tetraethylammonium (TEA), apamin, charybdotoxin, gliquidone or glibenclamide, are able to produce an antidepressant-like effect in mice[15–17] K^+ channel openers, such as minoxidil

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or cromakalim, however, induces a depressant-like effect. Studies also indicate that fluoxetine, a selective serotonin (5-HT) reuptake inhibitor generally used to treat depression, acts as a potent inhibitor of various ion channels, including K^+ channels.[18] The blockade of K^+ channels occurs by activation of several metabotropic receptors functionally coupled to the K^+ channel. This increases the release of 5-HT[19] and reduces[20] inhibitory tone, and is thought to be implicated in the mechanism of action of antidepressants. Moreover, the inhibition of K^+ currents may underlie the therapeutic effects of classical antidepressants, such as imipramine, clomipramine, citalopram and paroxetine.[21–25]

In addition, a recent study of Heurteaux *et al*.[26] demonstrated that the deletion of a gene coding for TREK-1, a class of two-pore domain K^+ channels, can lead to resistance to depression in animal models, suggesting that alterations in the functioning and regulation of these channels may alter mood and be a potential target for new antidepressants.

Peroxisome proliferator-activated receptor γ (PPARγ), as a member of the nuclear receptor superfamily of ligand-dependent transcription factors, plays an important role in insulin sensitivity, tissue homeostasis and the regulation of cellular functions.[27] PPARγ receptors are located in hippocampus, striatum, frontal cortex, hypothalamus, and many other brain areas. They are also located in glial cells and endothelial cells in the brain.[28,29] Indeed, PPARγ receptors may be implicated in the mechanism of action of antidepressants, since the anti-immobility effect of rosiglitazone, NP031115 and ARA014418 in the forced swimming test (FST) was reversed by GW9662.[30] In addition, Ahmed *et al*. demonstrated the antidepressant-like effect of rosiglitazone, a PPARgamma agonist, in the rat forced-swim and mouse tail-suspension (TST) tests.[31]

Since its introduction almost 20 years ago, the TST has become one of the most widely used models for assessing antidepressant-like activity in mice.[32] TST is based on the observation that rodents,[33,34] after initial escape-oriented movements, develop an immobile posture when placed in an inescapable stressful situation. In the TST, the stressful situation involves the haemodynamic stress of being hung in an uncontrollable fashion by their tail.[35] If antidepressant treatments are given prior to the test, the subjects will actively persist in escape-directed behaviours for longer periods of time than after vehicle treatment.

In view of the multitude of interactions between the L-arginine-NO pathway and K^+ channels, it is important to determine whether K^+ channels participate in the mechanism of the antidepressant-like effect of $(PhSe)_2$ in the mouse TST. Additional mechanisms of action may be involved in the antidepressant-like effect of $(PhSe)_2$. In addition, the present study was performed to examine the involvement of PPARγ receptors in the antidepressant-like effect of $(PhSe)_2$ in the mouse TST.

Materials and Methods

Animals

The behavioral experiments were conducted using male adult Swiss mice (25–35 g) maintained at 22–25°C with free access to water and food, under a 12:12 hour light/dark cycle, with lights on at 6:00 a.m. All manipulations were carried out between 08.00 a.m. and 04.00 p.m. All procedures were performed according to protocols approved by the Institutional Committee for Use and Care of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1996). The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, the Federal University of Santa Maria, Brazil. The same groups of mice were used in the tail suspension and locomotor activity tests.

Tail-suspension test

The total duration of immobility induced by tail suspension was measured according to the method described by Steru *et al*.[36] Immobility time defined as the absence of escape-oriented behaviours, such as swimming, was scored over 6 min, as previously described.[37,38]

Open-field test

To assess the possible effects of $(PhSe)_2$ on locomotor and exploratory activities, mice were evaluated in the open-field test (OFT). The open-field was made of plywood and surrounded by walls 30 cm in height. The floor of the open field, 45 cm in length and 45 cm in width, was divided by masking tape markers into nine squares (three rows of three). Each animal was placed individually at the centre of the apparatus and observed for 6 min to record the locomotor (number of segments crossed with the four paws).[39]

Intracerebroventricular injection technique

K^+ channel openers and inhibitors were administered to mice in a single injection of 5 μl by the intracerebroventricular (i.c.v.) route, directly into the lateral ventricle, as previously described,[40] with the bregma fissure as a reference. The i.c.v. administration was performed under light isoflurane anesthesia. Briefly, a 0.4 mm external diameter hypodermic needle attached to a cannula, which was linked to a 25 μl Hamilton syringe, was inserted perpendicularly through the skull and no more than 2 mm into the brain of the mouse. The injection was given over 30 s, and the needle remained in place for another 30 s in order to avoid reflux of the substances injected. The injection site was 1 mm to the right or left of the midpoint on a line drawn through to the anterior base of the ears. To ascertain that the drugs were administered exactly into the cerebral ventricle, the brains were dissected and examined macroscopically after the test.

Drugs

$(PhSe)_2$ was prepared and characterised by the method previously described.[41] Analysis of the ^1H NMR and ^{13}C NMR spectra showed analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of $(PhSe)_2$ (99.9%) was determined by GC/HPLC. All other chemicals were of analytical grade and obtained from standard commercial suppliers. $(PhSe)_2$ was dissolved in canola oil. The following drugs were used: tetraethylammonium (TEA), 2-chloro-5-nitro-N-phenylbenzamide (GW 9662), minoxidil,

apamin (Sigma Chemical Co, USA), charybdotoxin, cromakalim and glibenclamide (Tocris Cookson, Ballwin, MO, USA). Cromakalim was dissolved in saline with 10% Tween 80, whereas all the other drugs were dissolved in isotonic (NaCl 0.9%) saline solution immediately before use. Appropriate vehicle-treated groups were simultaneously assessed. Drugs were administered by i.c.v. route, in a volume of 5 μl per mouse, except $(PhSe)_2$, which was administered by peroral (p.o.) route in a constant volume of 10 ml/kg body weight.

The doses of $(PhSe)_2$ (1 mg/kg, a subeffective dose, and 5 mg/kg, an effective dose) and the route of administration (per oral) were selected based on a previously published study.[12] The i.c.v. route and doses of K^+ channel inhibitors and openers were also chosen based on a previous study.[16]

Treatments

Effects of K^+ channel inhibitors on the antidepressant-like action of $(PhSe)_2$ in mice

Animals were pretreated by i.c.v. route with subeffective doses of TEA (a non-specific inhibitor of K^+ channels, 25 pg/site), glibenclamide (an ATP-sensitive K^+ channel inhibitor, 0.5 pg/site), charybdotoxin (a large- and intermediate-conductance calcium-activated K^+ channel inhibitor, 25 pg/site) and apamin (a small conductance calcium-activated K^+ channel inhibitor, 10 pg/site) or vehicle.[16] Animals received a single oral administration of $(PhSe)_2$ (1 mg/kg, p.o., a subeffective dose) 30 min before the TST and OFT.

Effects of K^+ channel openers on the antidepressant-like action of $(PhSe)_2$ in mice

Distinct groups of animals were treated with K^+ channel openers, cromakalim and minoxidil (10 μg/site, i.c.v.)[16] or vehicle 30 min before $(PhSe)_2$ (5 mg/kg, an effective dose) administration. Mice were tested in the TST and OFT 30 min after $(PhSe)_2$ administration. Doses of $(PhSe)_2$ were chosen based on experiments previously performed in our resrach group.[12]

Effects of PPARγ receptors on the antidepressant-like action of $(PhSe)_2$ in mice

Mice were pre-treated with GW 9662, a PPARγ antagonist (10 μg/site, i.c.v., a dose that produces no effect in the TST).[30] After 15 min, $(PhSe)_2$ (5 mg/kg, an effective dose) or vehicle (canola oil) was injected and 30 min later the TST and OFT were carried out.

Statistical analysis

All experimental results are given as the mean ± SEM. Comparisons between experimental and control groups were performed by two-way ANOVA (inhibitors of K^+ channels, openers of K^+ channel, GW 9662 and diabetic x $(PhSe)_2$), followed by Newman–Keuls' test for post-hoc comparison when appropriate. A value of $P < 0.05$ was considered to be significant. Main effects are presented only when interaction was not significant.

Results

Effect of K^+ channel inhibitors on the antidepressant-like action of $(PhSe)_2$ in mice

The results depicted in Figure 1 show the combined effect of TEA (25 pg/site, i.c.v.) and $(PhSe)_2$ (1 mg/kg, a subeffective dose, p.o.) in the TST. Combined administration of TEA and $(PhSe)_2$ caused a decrease in the immobility time in the TST ($F_{1,24} = 18.37$, $P < 0.0003$). No significant effect was observed in the number of crossings ($F_{1,24} = 0.45$, $P < 0.5087$) in the OFT (Table 1).

Figure 1 shows that the combined administration of glibenclamide (0.5 pg/site, i.c.v.) and $(PhSe)_2$ (1 mg/kg, p.o.) did not alter the immobility time in the TST ($F_{1,24} = 0.90$, $P < 0.3527$). The number of crossings ($F_{1,24} = 0.16$,

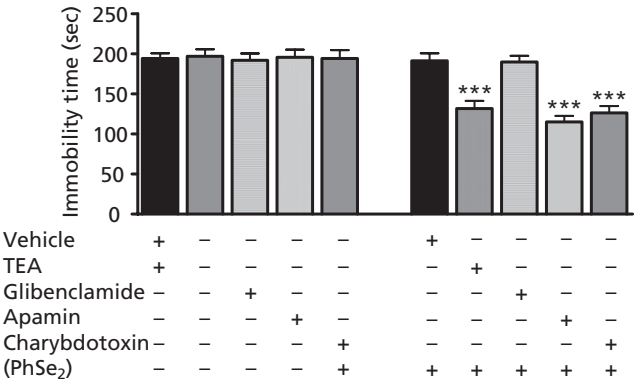

Figure 1 Effect of tetraethylammonium, glibenclamide, apamin or charybdotoxin in potentiating the action of a subeffective dose of $(PhSe)_2$. Tetraethylammonium (TEA) dosed at 25 pg/site, i.c.v., glibenclamide at 0.5 pg/site, i.c.v., apamin at 10 pg/site, i.c.v., charybdotoxin at 25 pg/site, i.c.v., $(PhSe)_2$ at 0.1 mg/kg, p.o. Values are expressed as mean ± SEM. ($n = 7$ mice/group). Data were analysed by two-way analysis of variance (ANOVA) followed by Newman–Keuls test. ***$P < 0.01$ compared to the vehicle group pretreated with $(PhSe)_2$.

Table 1 Effect of tetraethylammonium, glibenclamide, charybdotoxin, apamim, $(PhSe)_2$ or combined administration of $(PhSe)_2$ with K^+ channel inhibitors on the number of crossings in the OFT

Test	Number of crossings
Vehicle control	74.19 ± 5.95
Charybdotoxin	75.43 ± 5.10
$(PhSe)_2$	77.79 ± 7.79
Charybdotoxin + $(PhSe)_2$	80.83 ± 4.10
Vehicle control	73.61 ± 5.3
Apamim	72.99 ± 7.97
$(PhSe)_2$	74.66 ± 7.77
Apamim + $(PhSe)_2$	66.09 ± 8.35
Glibenclamide + $(PhSe)_2$	72.00 ± 7.09

Tetraethylammonium (TEA) dosed at 25 pg/site, i.c.v., glibenclamide at 0.5 pg/site, i.c.v., charybdotoxin at 25 pg/site, i.c.v., apamim at 10 pg/site, i.c.v., $(PhSe)_2$ at 1 mg/kg, i.p. Values are expressed as mean ± SEM. ($n = 7$ mice/group). Data were analysed by two-way analysis of variance (ANOVA) followed by Newman–Keuls test.

$P < 0.6912$) was unmodified by the administration of both drugs (Table 1).

Figure 1 demonstrates that the combined administration of apamin (10 pg/site, i.c.v.) and $(PhSe)_2$ (1 mg/kg, a subeffective dose, p.o.) was effective in decreasing the immobility time in the mouse TST ($F_{1,24} = 11.48$, $P < 0.0024$). The combined administration of $(PhSe)_2$ with the K^+ channel inhibitor, apamin (10 pg/site, i.c.v.), did not produce any effect on the number of crossings ($F_{1,24} = 1.98$, $P < 0.1722$) in the OFT (Table 1).

The results in Figure 1 show that the combined administration of charybdotoxin (25 pg/site, i.c.v.) and $(PhSe)_2$ (1 mg/kg, a subeffective dose, p.o.) was effective in decreasing the immobility time ($F_{1,24} = 14.10$, $P < 0.001$) in the mouse TST. The administration of $(PhSe)_2$ with charybdotoxin did not modify the number of crossings ($F_{1,24} = 0.06$, $P < 0.816$) in the OFT (Table 1).

Effect of K^+ channel openers on the antidepressant-like action of $(PhSe)_2$ in mice

Figure 2 shows the effect of pretreatment with cromakalim (10 μg/site, i.c.v.) in the antidepressant-like action of $(PhSe)_2$ (5 mg/kg, p.o.) in the mouse TST. Cromakalim did not reverse the reduction of the immobility time produced by $(PhSe)_2$ (5 mg/kg, p.o.) ($F_{1,24} = 1.86$, $P < 0.1850$). No significant difference was observed in the number of crossings ($F_{1,24} = 0.01$, $P < 0.9119$) in the OFT (Table 2).

The results in Figure 2 demostrate the effect of pretreatment with minoxidil (10 μg/site, i.c.v.) on the antidepressant-like action of $(PhSe)_2$ (5 mg/kg, p.o.) in the mouse TST. Minoxidil reversed the reduction of the immobility time produced by $(PhSe)_2$ (5 mg/kg, p.o.) ($F_{1,24} = 3.82$, $P < 0.047$). No significant difference was observed in the number of crossings ($F_{1,24} = 0.58$, $P < 0.4544$) in the OFT (Table 2).

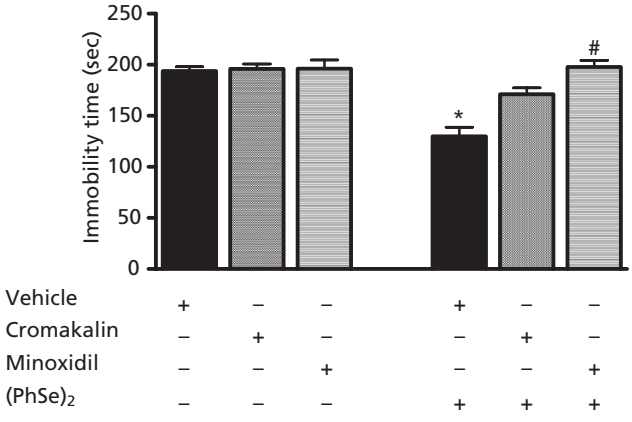

Figure 2 Effect of pretreatment of mice with cromakalim or minoxidil on the action of an effective dose of $(PhSe)_2$. Cromakalim dosed at 10 μg/site, i.c.v., minoxidil at 10 μg/site, i.c.v., $PhSe)_2$ at 5 mg/kg, p.o. Assessment by measurement of the immobility time in the tail-suspension test. Values are expressed as mean ± SEM. ($n = 7$ mice/group). Data were analysed by two-way analysis of variance (ANOVA) followed by Newman–Keuls test. $^*P < 0.01$ compared to the vehicle/vehicle group. $^{\#}P < 0.01$ compared to the vehicle group pretreated with cromakalim or minoxidil.

Table 2 Effect of cromakalim (10 μg/site, i.c.v.), minoxidil (10 μg/site, i.c.v.), $(PhSe)_2$ (5 mg/kg, i.p.) or combined administration of $(PhSe)_2$ with cromakalim or minoxidil on the number of crossings in the OFT

Treatments	Number of crossings
Vehicle control	69.80 ± 6.65
Cromakalim	71.90 ± 9.00
$(PhSe)_2$	72.06 ± 7.07
Cromakalim + $(PhSe)_2$	74.00 ± 7.65
Vehicle control	70.93 ± 9.10
Minoxidil	74.10 ± 8.90
$(PhSe)_2$	77.91 ± 7.89
Minoxidil + $(PhSe)_2$	70.29 ± 7.23

Cromakalim dosed at 10 μg/site, i.c.v., minoxidil at 10 μg/site, i.c.v., $(PhSe)_2$ at 5 mg/kg, i.p. Values are expressed as mean ± SEM. (n = 7 mice/group). Data were analysed by two-way analysis of variance (ANOVA) followed by Newman–Keuls test.

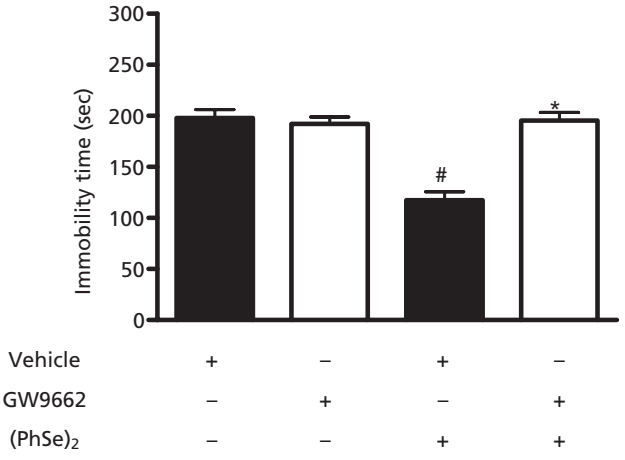

Figure 3 Effect of pretreatment of mice with GW9662 on the action of an effective dose of $(PhSe)_2$. Effect assessed by measurement of immobility time in the tail-suspension test test. GW9662 dosed at 10 μg/site, i.c.v., $(PhSe)_2$ at 1 mg/kg, p.o. Values are expressed as mean ± SEM. ($n = 7$ mice/group). Data were analysed by two-way analysis of variance (ANOVA) followed by Newman–Keuls test. $^{\#}P < 0.01$ compared to vehicle-treated mice; $^*P < 0.01$ compared to the $(PhSe)_2$ group.

Effect of PPARγ on the antidepressant-like action of $(PhSe)_2$ in mice

The results depicted in Figure 3 show the effect of pretreatment with GW 9662, a PPARγ antagonist (10 μg/site, i.c.v., a dose that produces no effect in the TST), on the antidepressant-like action of $(PhSe)_2$ (5 mg/kg, p.o.) in the TST. GW 9662 was effective in reversing the reduction in the immobility time produced by $(PhSe)_2$ (5 mg/kg, p.o.) ($F_{1,24} = 28.59$, $P < 0.001$). No significant effect was observed in the number of crossings ($F_{1,24} = 0.45$, $P < 0.5087$) in animals treated with both drugs in the OFT (Table 3).

Discussion

The results of the present study demonstrate that the inhibition of different types of K^+ channels enhance the antidepressant-

Table 3 Effect of treatment with $(PhSe)_2$, GW9662 or vehicle in mice on the number of crossings in the open-field test

Treatments	Number of crossings
Vehicle control	72.45 ± 9.70
$(PhSe)_2$	74.94 ± 9.24
GW9662	79.11 ± 5.90
GW9662 + $(PhSe)_2$	75.19 ± 7.33

$(PhSe)_2$ dosed at 5 mg/kg, i.p., GW9662 at 10 μg/site, i.c.v. Values are expressed as mean ± SEM. ($n = 7$ mice/group). Data were analysed by two-way analysis of variance (ANOVA) followed by Newman–Keuls test.

like effect of $(PhSe)_2$ in the mouse TST, a widely used animal model of antidepressant activity.[42,43] Treatment of mice with pharmacological compounds able to block different types of K^+ channels, such as TEA, charybdotoxin and apamin, caused a decrease in the immobility time in the TST when administered in combination with a subeffective dose of $(PhSe)_2$. The combination of these behaviorally inactive treatments provoked a robust reduction in the immobility time, indicative of an antidepressant-like behavioral profile. In addition, the combined administration of glibenclamide and $(PhSe)_2$ did not alter the immobility time in the TST, demostrating that ATP-sensitive K^+ channel is not involved in the antidepressant-like effect of $(PhSe)_2$. Pretreatment of mice with minoxidil, but not with cromakalin, both K^+ channel openers, prevented the antidepressant-like effect of an effective dose of $(PhSe)_2$. These results suggest the existence of an important link between K^+ channels and the mechanism of action of $(PhSe)_2$. These results are in accordance with previous findings that demonstrated the involvement of K^+ channels in the action of antidepressant drugs as fluoxetine[17] and sertarline.[16]

Locomotor performance in an OFT may reflect activation of a neural system different from the subserving struggling activity in the TST. However, compounds which increase ambulatory behaviour in general are also expected to cause hyperactivity in the OFT, and to reduce immobility in the depressive test, such as a 'false positive'.[44] Therefore, in order to exclude the possibility that the effect of K^+ channel openers and inhibitors in the TST is a reflection of a generalised increase in locomotor activity, mice were also evaluated in an OFT for ambulation. However, the effect of K^+ channel openers and inhibitors in increasing the behavioral response to $(PhSe)_2$ in the TST was not due to a non-specific locomotor stimulant effect of the drug combination. Indeed, the results of the OFT indicate that neither K^+ channel openers nor inhibitors, alone or administered in combination with $(PhSe)_2$, altered the locomotor activity. Therefore, the antidepressant-like effect of $(PhSe)_2$ combined with K^+ channel openers and inhibitors that has been demonstrated in this study cannot be attributed to general hyperactivity.

In this study, we showed that GW9662, a PPARγ antagonist, reversed the effects of $(PhSe)_2$ in the mouse TST. It appears that the modulation of PPARγ receptors by $(PhSe)_2$ plays a role in the antidepressant-like effect of this drug in the TST. In this context, Rosa and collaborators reported an antidepressant-like effect of thiadiazolidinone NP031115 by involvement of PPARγ in the FST.[30] PPARγ receptors are an emerging target in pharmacology, with promising effects in many diseases such as stroke,[45] Parkinson's disease,[46] multiple sclerosis[47] and amyotrophic lateral sclerosis.[48] Despite this growing interest in establishing the possible involvement of PPARγ in diseases related to the central nervous system (CNS), there is little information regarding the participation of these receptors in depression.

$(PhSe)_2$ is a highly lipophylic compound and therefore exhibits a concentration–time profile characterised by an early peak concentration and rapid distribution from blood to the CNS, where it exerts its pharmacological and toxicological effects.[49] Based on these data, we believe that $(PhSe)_2$ is easily dialysed inside the cell in order to activate these nuclear receptors. However, we do not rule out the possibility of some indirect effect.

The Pro12Ala polymorphism of PPARγ has been associated with decreased obesity, insulin resistance, type 2 diabetes and other age-associated diseases such as cognitive impairment, hypertension, cancer and osteoarthritis.[50–52] Each of these diseases had been linked to depression. Moreover, there is also an association between Pro12 Ala polymorphism in PPARγ2 and longevity. Recently, Ji-Rong and collaborators found that among Chinese nonagenarians and centenarians, the Pro12Ala polymorphism in PPARγ2 was associated with depression and that the 12Ala gene may be a factor for decreased depression.[53]

Conclusion

The present study extends literature data regarding the antidepressant-like action of $(PhSe)_2$ in the mouse TST. Some evidence for the involvement of some types of K^+ channels and PPARγ receptors in the antidepressant-like effect of $(PhSe)_2$ was also reported.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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