Intrastriatal gene delivery of GDNF persistently attenuates methamphetamine self-administration and relapse in mice

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Abstract

Relapse of drug abuse after abstinence is a major challenge to the treatment of addicts. In our well-established mouse models of methamphetamine (Meth) self-administration and reinstatement, bilateral microinjection of adeno-associated virus vectors expressing GDNF (AAV-Gdnf) into the striatum significantly reduced Meth self-administration, without affecting locomotor activity. Moreover, the intrastriatal AAV-Gdnf attenuated cue-induced reinstatement of Meth-seeking behaviour in a sustainable manner. In addition, this manipulation showed that Meth-primed reinstatement of Meth-seeking behaviour was reduced. These findings suggest that the AAV vector-mediated Gdnf gene transfer into the striatum is an effective and sustainable approach to attenuate Meth self-administration and Meth-associated cue-induced relapsing behaviour and that the AAV-mediated Gdnf gene transfer in the brain may be a valuable gene therapy against drug dependence and protracted relapse in clinical settings.

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Introduction

Glial cell line-derived neurotrophic factor (GDNF) has been widely tested as a potential therapeutic agent for the treatment of Parkinson’s disease (Tomac et al., 1995; Choi-Lundberg et al., 1997; Mandel et al., 1997; Kordower et al., 2000; Wang et al., 2002; Kirik et al., 2004), since GDNF was originally purified from a rat glioma cell-line supernatant as a trophic factor for embryonic midbrain dopamine neurons (Lin et al., 1993). Dopaminergic transmission from the ventral tegmental area to nucleus accumbens and prefrontal cortex plays an important role in the development of drug addiction and striatal dopaminergic transmission is critical for the conversion from drug use to drug abuse or habit formation (Everitt and Robbins, 2005; Di Ciano et al., 2008). Therefore, it is reasonable to postulate that GDNF may be involved in the development of drug addiction (Pierce and Bari, 2001). Indeed, GDNF has been identified as a critical modulator in the development of drug dependence in animal models (Messer et al., 2000; He et al., 2005; Niwa et al., 2007a, b; Lu et al., 2009). The manipulations that increase contents of GDNF in the striatum and nucleus accumbens attenuate acquisition of cocaine self-administration in rats (Green-Sadan et al., 2003, 2005). In contrast, the manipulations that decrease contents of GDNF in the brain facilitate drug-induced conditioned place preference and drug self-administration in rodent animals (Messer et al., 2000; Niwa et al., 2007a, b; Yan et al., 2007b). Previously, we have reported that a reduction of endogenous GDNF protein in heterozygous GDNF knockout mice (GDNF+/− mice) not only facilitates the acquisition of methamphetamine (Meth) self-administration, results in an upward shift in the dose–response curve and increases...
motivation to take Meth, but also leads to increased vulnerability to Meth-primed reinstatement and enduring vulnerability to cue-induced relapsing behaviour (Yan et al., 2007b). In a clinical setting, GDNF itself cannot be orally administered for the treatment of brain diseases. The next challenge we had was to investigate safe and permanent potentiation of GDNF expression only in the critical local brain areas. Adeno-associated viral (AAV) vector is one of the most useful tools for the delivery of therapeutic genes into the brain as a potential therapeutic strategy against brain diseases, because of its safety and sustainable expression in the dopaminergic transmission pathways in the brain (Wang et al., 2002; Eberling et al., 2009; Johnston et al., 2009; Kells et al., 2010). Recently, we used the AAV vector as a vehicle of the aromatic L-amino acid decarboxylase gene into the nigrostriatal pathway without adverse effects (Eberling et al., 2009; Su et al., 2009). In aged rats or Parkinsonian non-human primates, AAV-Gdnf-treated animals show clinical improvement and functional recovery in the nigrostriatal pathway without adverse effects (Eberling et al., 2009; Johnston et al., 2009; Kells et al., 2010). Currently, we used the AAV vector as a vehicle of the aromatic l-amino acid decarboxylase gene into the putamen of Parkinson’s disease patients for a clinical phase I study (Muramatsu et al., 2010). In this study, we determine effects of an intrastratal microinjection of the AAV-Gdnf on Meth self-administration, extinction and reinstatement of Meth-seeking behaviour in mice.

Materials and method

Subjects and drugs

Male C57BL/6j mice were aged 8 wk and weighed 20–25 g at the beginning of the experiments. They were kept in a regulated environment (23 ± 0.5 °C; 50 ± 0.5% humidity) with a 12-h light/dark cycle (lights on 09:00 hours). Water and food were available ad libitum. To minimize the number of animals in the experiments, a within-subjects design was used in Meth self-administration, extinction and reinstatement of Meth-seeking behaviour induced by either Meth-priming injection or presentation of Meth-associated cues in our experiments. All procedures followed the National Institute of Health Guidelines for the Care and Use of Laboratory Animals and were approved by the Nagoya University Animal Care and Use Committee.

Meth hydrochloride (Dainippon Pharmaceutical Ltd, Japan) was dissolved in sterile saline and self-administered at a dose of 0.1 mg/kg, infusion over 5 s (infusion volume 2.1 μl; Yan et al., 2006, 2007a).

The AAV vectors expressing GDNF

The AAV-Gdnf or AAV-EGFP was constructed and prepared as previously described (Wang et al., 2002). In the present study, the final particle titre for the intrastratal microinjection of the AAV-Gdnf and AAV-EGFP was 8.4 × 10^{14} and 6.4 × 10^{13} vector genome copies/ml, respectively.

Surgery for intravenous implantation of catheter and bilateral intrastratal injection of the AAV-Gdnf

Catheter implantation for Meth infusion

Naive mice were anaesthetized with pentobarbital sodium (50 mg/kg i.p.). Indwelling catheters were constructed of micro-silicone tubing (inner diameter, 0.50 mm; outer diameter, 0.7 mm; Imamura Co., Ltd, Japan) and polyethylene tubing (inner diameter, 0.50 mm; outer diameter, 0.8 mm). Incisions were made on the skin of the head and ventral neck and the right jugular vein was externalized. The end of the catheter was inserted into the jugular vein via a small incision and was secured to the vein and surrounding tissue with silk sutures. The exit port of the catheter passed subcutaneously to the top of the skull and was temporarily closed with a clamp.

Bilateral intrastratal microinjection of the AAV-Gdnf and AAV-EGFP vectors

Once the intravenous was successfully implanted as described above, the animals received bilateral microinjection of the AAV vectors into the striatum, according to the standard mouse brain coordinates (Franklin and Paxinos, 2007). Based on previous reports (Tomac et al., 1995; Chen et al., 2008), the AAV-Gdnf or AAV-EGFP vectors were bilaterally injected into the striatum (+0.9 mm anteroposterior, ±1.5 mm mediolateral, –3.0 and –2.0 mm dorsoventral) at two different depths through a 10 μl Hamilton syringe (Hamilton Company, USA) with a 33 gauge blunt hypodermic needle. At a lower site, the vectors were bilaterally injected in a volume of 1.0 μl/site over 2 min and the syringe needle was left in place for an additional 3 min. After the needle was pulled upward 1.0 mm (upper site), the vectors were bilaterally injected in a volume of 1.0 μl/site over 2 min and an additional 3 min for the needle in place. The burr hole was sealed with quick self-curing acrylic resin (Shofu Inc., Japan) after each injection.

Measurement of motility in a novel environment

Motility in a novel environment was measured in a transparent acrylic cage with a black Plexiglas floor (45 × 45 × 40 cm) using infrared counters (Scanet SV-40; MELQUEST, Japan). Two weeks after recovering from the bilateral intrastratal microinjection of the AAV-Gdnf or AAV-EGFP vectors, the two groups of mice (AAV-Gdnf and AAV-EGFP) were placed in the centre of the cage and allowed to move freely for 60 min. Locomotion and rearing were analysed to examine effects of the intrastratal microinjection of the AAV-Gdnf or AAV-EGFP vector on motility in general in mice.

Immunohistochemical staining for GDNF

Brain sections (16 μm) were cut on a cryostat, thaw-mounted on Silane-coated slides and stored at –80 °C.
until used. The brain sections were permeabilized with 0.1% Triton X-100, blocked with 1% bovine serum albumin and incubated with the mouse monoclonal antibody against GDNF (R&D Systems, USA) at 4°C overnight. To detect specific signals, the brain sections were incubated with CF594-conjugated secondary antibodies (Biotium, USA) for 2 h at room temperature. Images were captured and the density was evaluated with fluorescence microscopy (BZ9000; Keyence, Japan).

Meth self-administration, extinction and reinstatement of Meth-seeking behaviour

**Apparatus**

The standard mouse operant conditioning chambers (ENV-307A; Med Associates, USA) used in the current study were described previously (Yan et al., 2006, 2007a; Yan and Nabeshima, 2009).

**Meth self-administration**

After a 2-wk interval from the microinjection of the AAV-Gdnf or AAV-EGFP vectors into the striatum, the mice were subjected to daily 3-h sessions of Meth self-administration under a fixed ratio (FR) schedule of reinforcement. Throughout each session of self-administration, the house lights were illuminated and cue- and hole-lamps indicated the availability of Meth. Once the mice made nose-poke responses in the active hole, the cue- and hole-lamps were turned off and Meth (0.1 mg/kg, infusion) was delivered over 5 s followed by a 5-s time-out period. Responses in the active hole during the time-out period and in the inactive hole had no programmed consequences but were recorded. Self-administration was initially under an FR1 schedule of Meth reinforcement. Once the mice made 60% active nose pokes on average, an FR2 schedule of Meth reinforcement was introduced until the mice acquired stable Meth self-administration behaviour (deviations of <15% of the mean of active responses in three consecutive training sessions).

**Extinction**

The mice were then subjected to 8–16 daily 3-h sessions of extinction before the Meth-primed reinstatement test and then 3–6 daily 3-h sessions of extinction before the cue-induced reinstatement test until they met the extinction criterion (<15 active responses or 25% of active responses in the stable phase of self-administration in two consecutive sessions). The number of extinction training sessions for each mouse largely varied in the same treatment of group. Throughout the extinction session, the house light was on. The Meth-associated cue- and hole-lamps, and the pump for Meth infusion, were turned off. Therefore, nose-poke responses into the previously active hole resulted in neither an infusion of Meth nor Meth-associated cues (cue- and hole-lamps and pump noise for Meth infusion).

**Meth-primed reinstatement**

Once the extinction criterion was met, the animals were first subjected to a 3-h session of the operant test 30 min after the injection (i.p.) of saline as a control for the Meth-primed reinstatement. From the next day, the mice were subjected to daily 3-h tests for Meth-primed reinstatement 30 min after the i.p. injection with increasing doses of Meth (0.2, 0.4, 1.0 or 2.0 mg/kg, each dose for one daily 3-h session). All of mice were tested with each dose of Meth for drug-primed reinstatement on different days, but there was no extinction training between the tests. This is because: (1) different to drug-primed instatement in rats, drug-primed reinstatement in mice is transient; (2) it takes a much longer time for mice to be extinguished from drug self-administration than that in rats. The Meth-primed reinstatement tests were conducted under the same conditions as in the extinction sessions, in which neither Meth infusions nor Meth-associated cues were available after nose-poke responses into a previously active hole. Nose-poke responses in the previously active or inactive hole were counted as active and inactive, respectively.

**Cue-induced reinstatement**

After testing Meth-primed reinstatement, the same group of animals was subjected to extinction training once again. Once the extinction criterion was met, the animals were subjected to cue-induced reinstatement for the first time (the first test). Two months later, the same group of animals was subjected to cue-induced reinstatement for the second time (the second test). The cue-induced reinstatement tests were conducted under the same conditions as the Meth self-administration under the FR2 schedule, except that Meth was unavailable throughout the testing session. Nose-poke responses in the previously active or inactive hole were counted as active and inactive, respectively.

**Data analysis**

All data were expressed as the mean ± S.E.M. The data of GDNF densities, locomotor activities and total Meth intake between AAV-Gdnf and AAV-EGFP-treated mice were analysed with Student’s t-test. A two-way analysis of variance (ANOVA) with (or without) repeated measures was performed for the difference in either active or inactive nose-poke responses between the AAV-Gdnf and AAV-EGFP-treated mice during Meth self-administration, extinction training, Meth-primed and cue-induced reinstatement of Meth-seeking behaviour, followed post hoc by Bonferroni’s multiple
comparison test. In all cases, a significant difference was set at \( p < 0.05 \).

### Results

**Enhancement of GDNF expression in the dorsal striatum of the AAV-Gdnf-treated mice**

Figure 1a indicates the placement of cannulae for the intrastriatal microinjection of the AAV-Gdnf or AAV-EGFP vectors into the mouse brain. Figure 1b shows that the expression level of GDNF protein was clearly enhanced in the striatum 2 wk after the intrastriatal microinjection of the AAV-Gdnf vectors as compared to that after the microinjection of AAV-EGFP vectors. The densities of GDNF expression were 47.1±0.35, 137.1±5.06 in the striatum of AAV-EGFP and AAV-Gdnf, respectively, indicating that GDNF content increased significantly in the striatum by microinjection of AAV-Gdnf (Student’s t test, \( p < 0.001 \), d.f. = 41, \( t = 4.08 \)). To investigate the effects of the intrastriatal microinjection of AAV-Gdnf and AAV-EGFP vectors on behaviour in general, the motility in a novel environment was measured for locomotion and rearing, as the motor issue and exploratory motivation, respectively. Neither locomotion nor rearing during a 60-min period of observation differed significantly between the AAV-Gdnf (locomotion: 28.223.7±1978.0 counts; rearing: 526.5±52.9 counts, \( N = 6 \)) and AAV-EGFP-treated mice (locomotion: 24.539.6±976.5 counts; rearing: 542.4±49.9 and 526.5±130.0 counts, \( N = 6 \); Student’s t test, \( p = 0.94 \), d.f. = 10, \( t = -1.67 \) for locomotion; \( p = 0.415 \), d.f. = 10, \( t = 0.220 \) for rearing). These results indicate that microinjection of AAV-Gdnf has no significant influence on the general locomotion and exploratory motivation system in mice.

**Attenuation of Meth self-administration behaviour in AAV-Gdnf-treated mice**

Active and inactive nose-poke responses of AAV-Gdnf and AAV-EGFP-treated mice during Meth self-administration training are shown in Fig. 2a. Repeated two-way ANOVA analysis for active nose-poke responses (AAV vectors are between-subjects factors and training sessions are within-subjects factors) revealed that there was no significant difference in active nose-poke responses in the early phase of Meth self-administration (day 1–11) between the AAV-Gdnf and AAV-EGFP-treated mice. In the late phase of Meth self-administration, however, the active nose-poke responses to take Meth were lower in the AAV-Gdnf-treated mice than in the AAV-EGFP-treated mice (main effect of AAV vectors: \( F_{1,14} = 3.94, p < 0.05 \); main effect of training sessions: \( F_{15,210} = 28.39, p < 0.001 \); AAV vector × training session interaction: \( F_{15,210} = 2.31, p < 0.01 \)). There was no significant difference in inactive nose-poke responses between the AAV-Gdnf and AAV-EGFP-treated mice throughout Meth self-administration training (day 1–16). We have previously reported that total intake of Meth during drug self-administration affects the subsequent Meth-primed reinstatement (Yan et al., 2007a). After both groups of animals acquired stable Meth self-administration, the AAV-Gdnf-treated mice continued to be subject to Meth drug self-administration for four additional sessions to make two groups of animals with an equivalent total intake of Meth during drug self-administration training (Fig. 2a, day 17–20). As shown in Fig. 2b, the total intake of Meth during drug self-administration was 23.03±3.09 mg/kg in AAV-Gdnf-treated mice for 20 d and 22.86±3.22 mg/kg in AAV-EGFP-treated mice for 16 d (Student’s t test, \( p = 0.97 \), d.f. = 14, \( t = 0.04 \)). These observations suggest that the intrastriatal microinjection
of the AAV-Gdnf vectors is effective to attenuate the late phase of Meth self-administration behaviour in mice.

No difference in the process of extinction, but decrease of Meth-primed reinstatement in the AAV-Gdnf-treated mice

After the above-mentioned Meth self-administration, the same two groups of mice were subjected to 8–16 daily 3-h sessions of extinction training. As shown in Fig. 3a, repeated two-way ANOVA for active vs. inactive nose-poke holes in the same AAV vector treatment revealed that both groups of mice exhibit higher active than inactive nose-poke responses at the early phase of extinction training (for AAV-Gdnf-treated mice, main effect of within-subjects factor nose-poke holes: $F_{1,14} = 9.64, p < 0.01$; main effect of within-subjects factor training sessions: $F_{5,28} = 14.03, p < 0.001$; nose-poke hole x training session interaction: $F_{5,28} = 3.44, p < 0.01$. For AAV-EGFP-treated mice, main effect of within-subjects factor
nose-poke holes: $F_{1,14}=8.45$, $p<0.01$; main effect of within-subjects factor training sessions: $F_{5,70}=17.95$, $p<0.01$; nose-poke hole × training session interaction: $F_{5,70}=6.99$, $p<0.001$. However, there was no significant difference in active nose-poke responses between the AAV-Gdnf and AAV-EGFP-treated mice throughout extinction training (main effect of between-subjects factor AAV vectors: $F_{1,14}=1.82$, $p=0.20$; main effect of within-subjects factor training sessions: $F_{5,70}=21.99$, $p<0.001$; AAV vector × training session interaction: $F_{5,70}=0.61$, $p=0.69$). There was no significant difference in the number of sessions (d) taken for extinction training between the AAV-Gdnf and AAV-EGFP-treated mice (data not shown). When the extinction criteria were met, the two groups of mice were subjected to testing for Meth-primed reinstatement of drug-seeking behaviour. As shown in Fig. 3b, the AAV-EGFP-treated mice showed a clear dose-dependent tendency for drug-seeking behaviour induced by the i.p. priming injection of Meth. In contrast, the AAV-Gdnf-treated mice failed to show Meth-seeking behaviour after the priming injection of Meth at all doses examined (0.2–2.0 mg/kg i.p.). These data indicate that the intrastriatal microinjection of the AAV-Gdnf vectors may also be effective to attenuate Meth-primed reinstatement of Meth-seeking behaviour in mice.

**Long-lasting inhibition of cue-induced relapsing behaviour in the AAV-Gdnf-treated mice**

After testing for Meth-primed reinstatement, the same two groups of mice were subjected to 3–6 daily 3-h sessions of extinction training until the extinction criteria were met. When exposed to previous Meth-associated cues, both groups of mice showed cue-induced relapsing behaviour (Fig. 4a, two-way ANOVA, main effect of within-subjects factor cue and no-cue factors: $F_{1,26}=38.82$, $p<0.001$). Importantly, the number of active nose-poke responses was significantly reduced in the AAV-Gdnf-treated mice as compared to those in the AAV-EGFP-treated mice (Fig. 4a, two-way ANOVA, main effect of between-subjects factor AAV-Gdnf and AAV-EGFP treatments: $F_{1,26}=3.44$, $p<0.05$; cue × treatments interaction: $F_{1,26}=2.97$, $p=0.10$). Two months after this testing, the same two groups of mice were subjected to extinction training once again until the criteria were met. As shown in Fig. 4b, cue-induced reinstatement was significantly attenuated in the AAV-Gdnf-treated mice as compared to that in the AAV-EGFP-treated mice (Fig. 4b, two-way ANOVA, main effect of between-subjects factor AAV-Gdnf and AAV-EGFP treatments: $F_{1,26}=5.55$, $p<0.05$; cue × treatments interaction: $F_{1,26}=10.11$, $p<0.01$), although both groups of mice still showed cue-induced reinstatement of Meth-seeking behaviour (Fig. 4b, two-way ANOVA, main effect of within-subjects factor, cue and no-cue factors: $F_{1,26}=56.01$, $p<0.001$). These findings suggest that the inhibitory effects of intrastriatal AAV-Gdnf vectors on cue-induced reinstatement of Meth-seeking behaviour are long-lasting.

**Discussion**

GDNF has been considered as a potential therapeutic molecule to treat drug addiction (Ron and Janak, 2005; Niwa et al., 2008) and the AAV vectors are one of the most attractive gene delivery vehicles into the brain for the treatment of neurological diseases (Miyazaki et al., 2012). In our study, AAV-mediated delivery of a Gdnf gene into the striatum increased GDNF protein...
expression without activation of spontaneous locomotion (Fig. 1b). The increased GDNF significantly attenuated Meth self-administration. Moreover, the AAV-Gdnf vectors in the striatum persistently reduced cue-induced relapsing behaviour. In addition, this manipulation also showed a clear tendency to block Meth-primed reinstatement in mice. These findings suggest that the manipulation of GDNF expression via the AAV vectors may be valuable in a clinical setting for the treatment of drug addiction and relapse.

The AAV vectors have unique characteristics, including the lack of any disease associated with the wild-type virus, an ability to infect non-dividing cells, long-term transgene expression with a minimal inflammatory or immune response and the physical stability of viral particles (Miyazaki et al., 2012). Using the AAV vectors, several research groups have constructed different versions of the AAV vectors for the Gdnf gene transfer, most of which express functional GDNF protein in a sustained manner after local injections and produce a functional recovery of the impaired dopaminergic system in the brain (Mandel et al., 1997; Wang et al., 2002; Eberling et al., 2009; Kells et al., 2010). Consistently, our previous studies have demonstrated that the expression of GDNF protein driven by an AAV-mediated Gdnf vector could be detected in the striatum from week 2 after local injection to lifetime. Furthermore, the GDNF protein could be retrogradely transported to the dopaminergic neuron cell bodies in substantial nigra from the terminals in the striatum 4 wk after the injection. The nigral dopaminergic neurons are prevented from progressive degeneration, thereby contributing to behavioural improvement in a rat model of Parkinson’s disease (Wang et al., 2002). In the current study, the inhibitory effects of the AAV-Gdnf vectors into the striatum on cue-induced relapsing behaviour were sustained for at least 2 months in mice. Such persistently inhibitory effects of the AAV-mediated delivery of a Gdnf gene on cue-induced relapsing behaviour may result from a sustained expression of the AAV-Gdnf vectors in the nigra-striatal circuit after bilateral intrastratal microinjection. This observation is consistent with our previous findings that Gdnf+/− mice show an enduring vulnerability to cue-induced reinstatement of Meth-seeking behaviour (Yan et al., 2007b). In the present study, the bilateral intrastratal injection of the AAV-Gdnf vectors also decreased the late phase of Meth self-administration in mice (Fig. 2a).

It is unlikely that persistent inhibitory effects of bilateral intrastratal injection of the vector-mediated delivery of a GDNF gene on Meth self-administration and cue-induced reinstatement result from non-specific procedures of microinjection. First, there was no significant difference in locomotion and rearing after the bilateral intrastratal injection between AAV-Gdnf- and AAV-EGFP-treated mice. Second, there was no difference in extinction after the bilateral intrastratal injection between AAV-Gdnf- and AAV-EGFP-treated mice. This observation, however, seems to be in discrepancy with one previous report in which microinjection of an AAV-Gdnf vector into the ventral tegmental area potentiates extinction responding in Long Evens rats (Lu et al., 2009). One parsimonious explanation is that the difference may reflect a distinct role of the nigrostriatal pathway or ventral tegmental area–nucleus accumbens in extinction responding (injection into the striatum in our study vs. injection into the ventral tegmental area in the report of Lu et al. 2009). Chen et al. (2008) have recently reported that the expression of GDNF protein via an AAV-Gdnf vector in the dorsal striatum prevents neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced deficits in the striatal synaptic plasticity. These findings may provide a potential molecular mechanism by which bilateral intrastratal injection of the AAV-Gdnf vectors attenuated cue-induced reinstatement of Meth-seeking behaviour in our study, since it is well known that neurotoxic effects of Meth in the brain play an important role in the development of Meth addiction.

It has been well established that the nucleus accumbens and striatum have a distinct role in the development of drug addiction. The nucleus accumbens is well known to mediate the reinforcing effects of addictive drugs, whereas the striatum is critical to the transition from initial drug use to habitual drug abuse to compulsion (Everitt and Robbins, 2005). It has been postulated that, during the development of drug self-administration, neutral drug-conditioned environmental cues acquire a reinforcing property, which evokes drug craving and relapse. Previous studies have shown that the striatum is critical for cue-induced reinstatement of drug-seeking behaviour in animals (Di Ciano et al., 2008). Consistently, bilateral intrastratal injection of the AAV-Gdnf vectors persistently attenuated cue-induced reinstatement of Meth-seeking behaviour in mice. This phenomenon may reflect a specific role of the nigra-striatal dopaminergic transmission pathway in the cue-induced relapse or the late stage of drug dependence/addiction. In addition, previous studies have shown that over-expression of GDNF in the striatum and nucleus accumbens attenuates cocaine self-administration behaviour in rats (Green-Sadan et al., 2005). In agreement with these findings, in our current study, bilateral intrastratal injection of the AAV-Gdnf vectors significantly reduced the late phase of Meth self-administration or potentially blocked Meth-primed reinstatement.

Taken together, the bilateral intrastratal microinjection of the AAV-Gdnf vectors in the brain significantly attenuated Meth self-administration and cue-induced reinstatement of Meth-seeking behaviour in mice, without affecting either general locomotor activity or extinction. This suggests that increased expression of exogenous GDNF protein through the microinjection of AAV-Gdnf vectors in the brain may be a gene therapeutic strategy to treat drug dependence and relapse in a clinical setting.
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Statement of Interest

None.

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None.
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