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GM1 ganglioside enhances the rewarding properties of cocaine in rats

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ABSTRACT

GM1 pretreatment enhanced the rewarding properties of cocaine as assessed in the conditioned place preference paradigm. This effect was shown by the lower dosage of cocaine necessary to induce conditioning compared with rats receiving cocaine alone, as well as by the fewer number of sessions necessary to induce place preference. GM1 pretreatment did not modify the plasma level of cocaine, but it induced a significant increase in the brain cocaine level compared with animals receiving cocaine alone. In order to evaluate the possibility that GM1 pretreatment may alter the pharmacokinetic parameters of cocaine, the brain and plasma esterase activities, the plasma bound/free cocaine ratio and the brain blood barrier permeability to i.v. Evans Blue administration were assessed. None of these parameters was modified by the GM1 administration. In addition, GM1 (100 μM) did not alter the dopamine transporter inhibition induced by cocaine (10^{-7}–10^{-5} M), as determined by the uptake of [$^{3-}$H]-dopamine in the microsacs of nucleus accumbens. In conclusion, GM1 pretreatment, which did not have any effect *per se*, increased the rewarding effect of cocaine, a phenomenon correlated with a significant increase in the brain cocaine levels. The different pharmacokinetic parameters evaluated, as well as the inhibitory effect of cocaine on the dopamine transporter, were not modified by GM1, but it modifies the brain cocaine disposition. Thus, the mechanisms by which GM1 enhanced the rewarding effects of cocaine merit further study.

1. Introduction

Different lines of evidence, arising from both *in-vivo* and *in-vitro* studies, have pointed out that GM1 exerts neuroprotective, neurorestorative and antineurotoxic effects on neurotransmitter systems on the CNS, especially in dopaminergic pathways (see review from Hadjiconstantinou and Neff, 1998). Furthermore, exogenous gangliosides seem to facilitate the processes of neuronal plasticity and the antidepressive effects resulting from different pharmacological treatments. Gangliosides were observed to enhance and exert an accelerating antidepressive effect of desipramine in the forced swimming test, as well as on the down-regulation phenomenon of brain β-adrenergic receptors (Molina et al., 1989). Similarly, ganglioside pretreatment increased in mice the antidepressive effect of desipramine, mianserin, clomipramine, nialamide, and electroconvulsive shock, as assessed in the forced swimming test (Córdoba et al., 1990). Furthermore, GM1 attenuates the behavioral effects of long-term haloperidol administration in supersensitive rats (Perry et al., 2004).

As regards drugs of abuse, repeated GM1 administration attenuates the behavioral sensitization effects of ethanol (Bellot et al., 1996), and amphetamine (Bellot et al., 1997). Neuronal processes involved in the development of tolerance and sensitization to drugs of abuse, which represent the plastic phenomena from the brain rewarding circuit, are basically defined by the activity of the ventral tegmental area–nucleus accumbens dopaminergic pathways. Bearing in mind the effects of GM1 on the neuronal plasticity mentioned above, as well as the modulatory effects that GM1 exerts on the behavioral sensitization induced by repeated ethanol or amphetamine administration, the aim of the present study was to explore if GM1 pretreatment affects the rewarding effect of cocaine, by using the conditioning place preference paradigm. Furthermore, in order to investigate if GM1 pretreatment may modify the pharmacokinetic of cocaine, different parameters, such as plasma and brain cocaine levels; plasma bound/free cocaine ratio; plasma and brain esterase activity as well as the effect of GM1 on the brain blood barrier permeability to Evans Blue following i.v. administration were assessed. Finally, to evaluate if GM1 may potentiate the inhibitory effect of cocaine on the dopamine transporter, the uptake of [^{3}H]-dopamine in microsacs from nucleus accumbens was investigated using different cocaine concentrations.

2. Materials and methods

2.1. Animals

Male Wistar rats from our own colony, weighing 250–330 g, were used in this study. They were maintained at 22 ± 2 °C under a 12 h light–dark cycle (lights on at 07:00 AM) with free access to food and water. All animal studies were performed in compliance with the recommendations of the Ethics Committee of our School, which are

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based on the indications of the Guide for Care and Use of Laboratory Animals (National Research Council, USA, 1996). All efforts were made to minimize both animal suffering and the number of animals used.

2.2. Drugs and treatments

GM1 (dry powder, 98%) obtained from porcine brains, was kindly provided by TRB-Pharma, Buenos Aires, Argentina, and cocaine hydrochloride (Verardo Laboratories, Buenos Aires, Argentina) was dissolved in distilled water. All solutions were administered via i.p.

S-butyrylthiocholine iodide and acetylthiocholine iodide were purchased from Sigma Co. (USA).

[^{3}H]-dopamine (33.7 Ci/mmol) was from PerkinElmer, USA.

All other reagents used were of analytical grade.

Saline and GM1 (30 mg/kg) were administered 2 h before the corresponding cocaine injection (5 or 10 mg/kg) at volumes of 1 ml/kg.

2.3. Conditioning place preference procedure

The place conditioning procedure used in these experiments was similar to that described by Valdomero et al. (2006), and included an unbiased design. The apparatus for conditioned place preference comprised two compartments distinguished by different patterns on the floors and walls, separated by a third central neutral compartment which was connected to the outer compartments by guillotine doors. Sessions were conducted twice per day, with 5 h separating each one. Rats were injected with saline and confined to one of the outer compartments for 45 min. Five hours later, they received cocaine injections and were confined to the other outer compartment for 45 min. The day after the last place conditioning day, the testing session was carried out by placing the animal for 15 min in the central compartment, with free access to all three compartments. The time spent in each compartment was recorded by two experimenters who were always unaware of the drug treatment of the animals. To evaluate the influence of GM1 pretreatment on cocaine inducing conditioned place preference, different groups of rats were conditioned with either 5 or 10 mg/kg of cocaine and either 1, 2, 3 or 4 conditioned sessions were conducted. In order to evaluate a possible GM1 conditioning effect, another group of animals receiving GM1 was conditioned in the same way using 4 sessions. Place preference was evaluated as time spent in the drug-paired compartment relative to the total time spent in outer compartments [preference score = time in paired/(time in paired + time in non-paired compartment)].

2.4. Determination of brain and plasma cocaine levels by HPLC-UV

Different groups of rats were treated with saline or GM1, and 2 h later injected with cocaine (10 mg/kg). Thirty minutes after cocaine administration, the animals were decapitated, brains were quickly removed, and blood samples were collected in 4% NaF and immediately stored at −20 °C until analyzed. The brain and plasma cocaine levels were assessed by the HPLC procedure and UV detection (Valdomero et al., 2005, 2006).

2.5. Determination of plasma free cocaine levels

Plasma samples were centrifuged in an Amincon Ultra-4 (Centrifugal filter devices, Millipore, cut-off 3,000) at 7500 *g* for 25 min at 25 °C. Free cocaine levels were assayed in the ultrafiltrate fraction by the above-mentioned procedure.

2.6. Determination of brain and plasma esterase activity

Two hours after the corresponding saline or GM1 injections, animals were decapitated, brains quickly removed, and blood samples collected on heparin. Plasma samples were diluted 1:10 in phosphate buffer 0.1 M (pH 8.0), and brains were homogenized in the same buffer. Acetylcholinesterase and butyrylcholinesterase were measured in brain and plasma, respectively, according to Ellman et al. (1961). S-butyrylthiocholine iodide was used as a substrate for butyrylcholinesterase, and acetylthiocoline iodide for acetylcholinesterase determinations.

2.7. Blood–brain barrier permeability to i.v. Evans Blue administration

In order to evaluate a possible effect of GM1 on the blood–brain barrier permeability, different groups of animals received saline or GM1, and were injected 2 h later i.v. with Evans Blue (2% in water solution) and then decapitated after 30 min. Brains were homogenized in phosphate buffer saline and vortex after the addition of 60% trichloroacetic acid. Samples were then cooled for 30 min and centrifuged for the same time at 1000 *g*. The supernatant were measured at 610 nm for absorbance of the dye, according to Elmas et al. (2001). Results were expressed as μg Evans Blue/g fresh tissue.

2.8. Assay of [^{3}H]-dopamine uptake in microsacs from nucleus accumbens. Effect of GM1 on the inhibitory dopamine uptake induced by cocaine

Animals were sacrificed by decapitation and their brains removed to an ice-cooled dish for nucleus accumbens dissection. Chopped tissue was prepared by mincing the tissue to a fine paste with a scalpel. [^{3}H]-dopamine uptake assays were performed according to Izenwasser et al. (1990). The chopped tissue was suspended in a modified Krebs-HEPES buffer (127 mM NaCl, 5 mM KCl, 1.3 mM NaH_2PO_4, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 15 mM HEPES, 10 mM glucose, 1.0 mM ascorbic acid, 10 μM pargyline, pH 7.4). Then, aliquots of chopped tissue were put into test tubes (approximately 1.3 mg protein/tube) containing different concentrations of cocaine (10^{-4}, 10^{-5}, 10^{-6} or 10^{-7} M), or cocaine plus GM1 (100 μM) dissolved in oxygenated buffer (final volume of 800 μl), and incubated for 10 min at 37 °C. After incubation, 15 nM [^{3}H]-dopamine were added to each tube and incubated for 5 min. The assay was terminated by the addition of 2.5 ml of ice-cold buffer, and rapid vacuum filtration was performed over a Whatman GF/C glass fiber filter using a Brandel cell harvester. After 3 rinses with cold buffer, the filters were placed in scintillation vials with 0.2 N HCl and liquid scintillation cocktail. Radioactivity was determinated using a Packard Tri-Carb Analyzer. Total uptake was expressed as pmol [^{3}H]-dopamine/mg protein and the radioactivity of the other experimental tubes as percentage of total dopamine uptake.

2.9. Statistical analysis

The differences in behavioral scores were analyzed using a two-way ANOVA with drug pretreatment (saline or GM1) and the number of sessions as the independent variables. Pharmacokinetic data were analyzed using a one-way ANOVA (pretreatment). Post-hoc comparisons were made using the LSD Fisher test, with values of $P<0.05$ being considered as statistically significant.

3. Results

3.1. Effect of GM1 administration on the rewarding properties of cocaine in the conditioned place preference

Fig. 1 shows the effect of GM1 pretreatment on the conditioning effect of cocaine (5 mg/kg) in the conditioned place preference task,

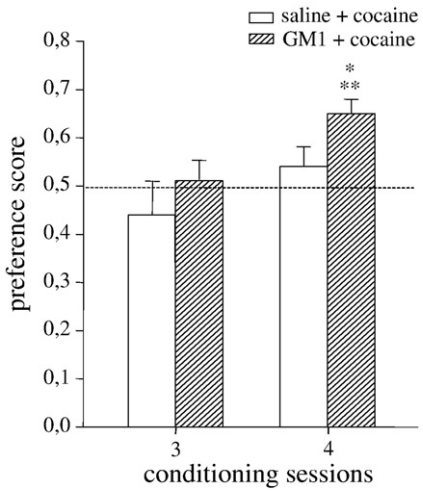

Fig. 1. Effect of GM1 pretreatment on cocaine (5 mg/kg) induced place conditioning. Bars represent means preference score ± S.E.M. from saline and GM1 pre-exposed animals conditioned with cocaine. Experimental groups were shaped by 8–10 rats each. The dashed line represents the preference score from animals conditioned with saline in both compartments (saline–saline group). $^{*}P<0.01$ vs. saline–saline group; $^{**}P<0.05$ vs. the respective saline–cocaine (LSD Fisher test).

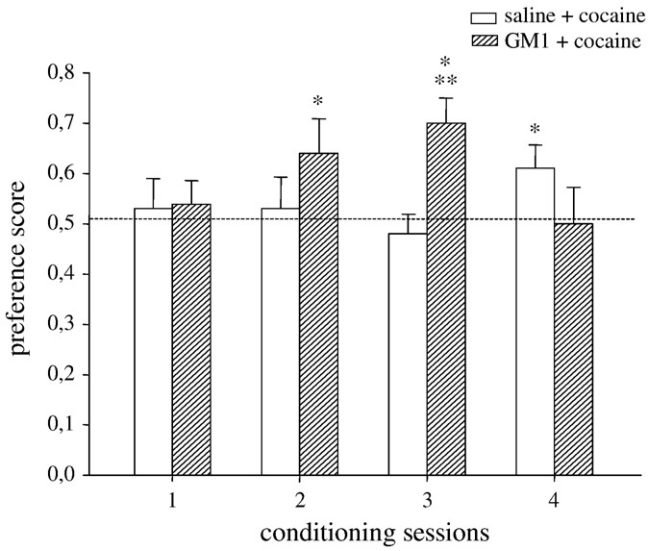

Fig. 2. Evaluation of the rewarding properties of cocaine (10 mg/kg) determined in the conditioned place preference paradigm after saline or GM1 pretreatment. Bars represent mean preference score ± S.E.M. ($n=10$–12 for saline and GM1 pretreated groups). The dashed line represents the preference score from animals conditioned with saline in both compartments (saline–saline group). $^{*}P<0.05$ or more vs. saline–saline group; $^{**}P<0.005$ vs. the respective saline–cocaine group.

using 3 or 4 conditioning sessions. In agreement with a previous report (Valdomero et al., 2006), this dose of cocaine was unable to induce place preference with a schedule of 4 sessions. However, GM1 pretreatment did enhance the effect of cocaine, since a significant conditioning effect was observed ($F_{1,32}=5.855$; $P<0.05$). For the 3 conditioning sessions used, none of the experimental groups showed place preference.

A cocaine dose of 10 mg/kg was assessed for different groups, using 1, 2, 3 or 4 conditioning sessions. Analysis of these data revealed a significant interaction (pretreatment × number of conditioning session; $F_{3,78}=3.099$, $P<0.05$). Results of experiments with cocaine alone showed a significant effect, but only for 4 conditioning sessions ($P<0.05$). However, GM1 pretreated groups showed a significant conditioning effect in experiments with 2 sessions ($P<0.05$) or 3 sessions ($P<0.01$), an effect that disappeared with 4 sessions, indicating a shift to the left in the sessions/effect curve (Fig. 2). Another experimental group realized with GM1 alone using 4 conditioned sessions did not show any conditioning effect (data not shown).

3.2. Effect of GM1 pretreatment on the plasma and brain cocaine levels

Following a single administration of 10 mg/kg of cocaine, plasma levels were analyzed in saline and GM1 pretreated animals. Although no significant differences between groups were found ($F_{1,17}=2.46$, N.S.) for plasma levels, a significant increase in brain cocaine content was detected in GM1 pretreated animals compared with those receiving cocaine alone [($F_{1,14}=7.01$; $P<0.05$), Table 1-a].

3.3. Determination of plasma bound and free cocaine levels

Determination of plasma bound and free cocaine levels following a single dose of 10 mg/kg showed no differences between GM1 pretreated animals compared with those receiving saline plus cocaine [$F_{1,9}=0.04$; N.S.], thus indicating that GM1 pretreatment did not affect the plasma bound/free cocaine ratio (Table 1-b).

3.4. Assessment of plasma and brain esterase activities following GM1 administration

Acetylcholinesterase and butyrylcholinesterase activities were measured in brain and plasma, respectively, for saline and GM1-treated animals. No significant differences between groups were found either acetylcholinesterase for activity ($F_{1,10}=0.69$, N.S.) or for butyrylcholinesterase activity ($F_{1,10}=0.01$, N.S.), thus demonstrating that GM1 did not alter the activity of these enzymes (Table 2).

3.5. Effect of GM1 pretreatment on the blood–brain barrier permeability to Evans Blue administration

Brain Evans Blue levels in saline or GM1 pretreated animals, expressed as μg/g fresh tissue, were 4.76 ± 0.38 ($n=11$) and 5.15 ± 0.69 ($n=9$), respectively ($F_{1,18}=0.30$, N.S.).

3.6. Effect of GM1 on the cocaine's inhibitory effect on [^{3}H]-dopamine uptake in microsacs from nucleus accumbens

The mean value of total [^{3}H]-dopamine uptake was 0.80 ± 0.03 pmol/mg protein ($n=3$). Cocaine inhibited the [^{3}H]-dopamine

Table 1
Effect of GM1 pretreatment on cocaine levels.

a. On the plasma and brain levels

Pretreatment	Plasma levels (ng/ml)	Brain levels (ng/g fresh tissue)
Saline	323 ± 19 ($n=10$)	1437 ± 130 ($n=12$)
GM1	384 ± 35 ($n=9$)	1936 ± 134[a] ($n=12$)

b. On the plasma bound and free cocaine levels

Pretreatment	Bound cocaine (ng/ml)	Free cocaine (ng/ml)	Bound cocaine (%)
Saline	341 ± 18 ($n=5$)	33.4 ± 8.3 ($n=5$)	90.6
GM1	393 ± 29 ($n=6$)	36.3 ± 10.7 ($n=6$)	91.6

Data are means ± S.E.M. Two hours after the corresponding saline or GM1 injection, animals were injected with cocaine (10 mg/kg) and 30 min later sacrificed for plasma and brain cocaine determination (a), or for plasma bound and free cocaine determination (b).

[a] Differs significantly from respective saline pretreated animals (LSD Fisher test, $P<0.05$).

Table 2
Determination of plasma and brain esterase activity.

Pretreatment	BuChE activity (μmol/l/min)	AChE activity (pmol/mg protein/min)
Saline	0.92 ± 0.06 (n = 6)	0.068 ± 0.004 (n = 6)
GM1	0.91 ± 0.11 (n = 6)	0.074 ± 0.006 (n = 6)

Data are mean ± S.E.M. Animals were injected with saline or GM1 and 2 h later sacrificed for esterase determination. No significant differences were detected between saline or GM1 treated groups.

uptake in a concentration dependent way, with a maximum effect seen at 10 μM. GM1 did not modify the inhibition of the [^{3}H]-dopamine uptake induced by cocaine (1.10^{-7} to 1.10^{-5} M).

4. Discussion

In a previous work, we described the rewarding effect of cocaine in rats, by employing a wide range of dosage (3–60 mg/kg i.p.), and using the conditioned place preference paradigm with a similar protocol as that defined in the present study. Doses of 10, 15 and 30 mg/kg, with a schedule of 4 conditioning sessions, showed significant rewarding effects of similar magnitudes, whereas lower or higher doses neither exhibited rewarding nor aversive effects (Valdomero et al., 2006).

In the current work, GM1 pretreatment, which had no effect *per se*, produced a significant increase of the rewarding effect induced by cocaine. Such an effect is shown by a shift to the left of the dose–response curve to cocaine in the conditioned place preference paradigm, since GM1 pretreated animals receiving a subthreshold dose of cocaine (5 mg/kg) exhibited a significant conditioned preference. In the same way, 10 mg/kg of cocaine, the lowest dose that induced place preference in rats in a schedule of 4 conditioning sessions, was able to elicit conditioning with only 2 and 3 conditioning sessions in GM1 pretreated animals. On the whole, these results demonstrated that GM1 pretreatment increase the capacity of cocaine to induce conditioned place preference, as well as accelerating the neuronal processes involved in the rewarding behavior. These effects kept correlation with a significant increase in the brain cocaine levels observed in the GM1 pretreated animals.

In order to explain the higher brain cocaine levels observed in GM1 pretreated animals, some pharmacokinetic parameters were determined. Since the principal route for cocaine metabolism involves hydrolysis of each of its two ester groups (O'Brien, 2001), we explored the possibility that GM1 administration might modify the brain and/or the plasma esterase activity. However, the results obtained indicated that GM1 administration did not alter the activities of these enzymes. On the other hand, serum albumin has the capacity to bind both gangliosides (Rebbaa and Portoukalian, 1995) and cocaine (Edwards and Bowles, 1988). In order to investigate the possibility that GM1 may exert a competitive effect on plasma binding sites, thus freeing more cocaine molecules, the plasma bound/free cocaine ratio was evaluated in animals treated with GM1 or saline previous to cocaine administration. Results from both bound and unbound plasma cocaine levels indicated that GM1 pretreatment did not significantly modify the bound/free cocaine ratio. Furthermore, in order to evaluate a possible effect of GM1 pretreatment on the permeability of the blood–brain barrier, we assessed the brain Evans Blue levels following an i.v. administration of the dye. However, the results obtained demonstrated that following injections the brain Evans Blue levels did not show significant differences between groups pretreated with GM1 or saline, indicating that GM1 did not alter the blood–brain barrier permeability to the dye.

Taken together, all the above results demonstrate that GM1 pretreatment enhanced the rewarding properties of cocaine, with this effect being correlated with a significant increase in the brain's cocaine levels. Furthermore, the determinations of some factors that may have affected the brain's cocaine levels (esterase's activity, plasma bound/free ratio, blood–brain barrier permeability) showed these parameters not to have been modified by GM1 administration. Thus, it can be postulated that GM1 alters the brain cocaine disposition, increasing the brain's capacity to bind cocaine. However, since these cocaine determinations were carried out in the whole brain, we have no evidence to ascertain if the binding was increased at unspecific sites or at specific sites related to the dopamine transporter. However, the in-vitro experiments carried out on microsacs from the nucleus accumbens in order to assess the effect of GM1 on the cocaine inhibitory effect of [^{3}H]-dopamine uptake, revealed no significant differences between samples incubated with GM1 plus cocaine or cocaine alone. Nevertheless, it should be taken into account that the in-vitro GM1 condition did not necessarily resemble the effects of its systemic administration.

In recent years, different lines of experimental evidence have provided increasing knowledge about the role of GM1 in the regulation of plastic neuronal processes and its interaction with neuronal factors, in particular with certain neurotrophins and/or their respective receptors. For example, it has been reported that GM1 is able to activate Trk receptors, an effect observed in fibroblast as well as in cultured cerebellar granule cells. Also, the activation of these receptors was shown to be mediated by a rapid and significant increase in the amount of neurotrophin-3, but not of other neurotrophins (Rabin et al., 2002). In addition, GM1 was demonstrated to be able to induce phosphorilation and activation of Trk and Erk in the brain (Duchemin et al., 2002), as well as to increase the activity of the phosphatidylinositol 3 (PI_3)-kinase pathway (Duchemin et al., 2008).

Another avenue to explore in order to explain the effect of GM1 on the rewarding properties of cocaine arises from the fact that repeated cocaine administration leads to an increase of the brain derived neurothrophic factor (BDNF) (Coraminas et al., 2007). Thus, it is possible that GM1 may promote the release and/or increase the effects of BDNF, by activating its main intracellular signaling mechanism involved in the psychostimulant processes related to the development of addiction. With respect to the GM1–BDNF interaction, it has been previously described that the capacity of BDNF to enhance the survival of cultured dopaminergic neurons from injury induced by 6-hydroxydopamine, was rendered efficacious with subthreshold amounts of BDNF in the presence of GM1 (Fadda et al., 1993).

In conclusion, the results of the present study demonstrate that GM1 administration both enhances and accelerates the initiation of rewarding processes, an effect that may be correlated with a significant rise in the brain's cocaine levels. The present study adds more evidence to the numerous studies that have demonstrated the different effects of gangliosides on the development and/or modulation of plastic neuronal processes, which in our case were related to the rewarding dopamine pathway. At present, however, the cellular and/or molecular mechanisms involved in these effects are still unclear, and consequently, should be the focus of additional studies.

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References

Bellot, R.G., Camarini, R., Vital, M.A.B.F., Palermo-Neto, J., Leyton, V., Frussa-Filho, R., 1996. Monosialogangliosides attenuates the excitatory and behavioral sensitization effects of ethanol. Eur. J. Pharmacol. 313, 175–179.

Bellot, R.G., Vital, M.A.B.F., Palermo-Neto, J., Frussa-Filho, R., 1997. Repeated monosialoganglioside administration attenuates behavioral sensitization to amphetamine. Brain Res. 747, 169–172.

Coraminas, M., Roncero, C., Ribases, M., Castells, X., Casas, M., 2007. Brain derived neurotrophic factor (BDNF) and its intracellular signaling pathways in cocaine addiction. Neuropsychobiology 55, 2–13.
Córdoba, N.E., Basso, A.M., Molina, V.A., Orsingher, O.A., 1990. Gangliosides enhance the anti-immobility response elicited by several antidepressant treatments in mice. Psychopharmacology 100, 555–557.
Duchemin, A.M., Ren, Q., Mo, L., Neff, N.H., Hadjiconstantinou, M., 2002. GM1 ganglioside induces phosphorilation and activation of Trk and Erk in brain. J. Neurochem. 81, 697–707.
Duchemin, A.M., Ren, Q., Neff, N.H., Hadjiconstantinou, M., 2008. GM1-induced activation of phosphatidylinositol 3-kinase: involvement of Trk receptors. J. Neurochem. 104, 1466–1477.
Edwards, D.J., Bowles, S.K., 1988. Protein binding of cocaine in human serum. Pharm. Res. 5, 440–442.
Ellman, G.L., Courtney, K.D., Andres Jr., V., Feather-Stone, R.M., 1961. A new and rapid colorimetric determination of acetylcholinesterase activity. Biochem. Pharmacol. 7, 88–95.
Elmas, I., Küçük, M., Kalayci, R.B., Cevik, A., Kaya, M., 2001. Effects of profound hypothermia on the blood–brain barrier permeability in acute and chronically ethanol treated rats. Forensic Sci. Int. 119, 212–216.
Fadda, E., Negro, A., Facci, L., Skaper, S.D., 1993. Ganglioside GM1 cooperates with brain-derived neurotrophic factor to protect dopaminergic neurons from 6-hydroxydopamine-induced degeneration. Neurosci. Lett. 159, 147–150.
Hadjiconstantinou, M., Neff, N.H., 1998. GM1 ganglioside: in vivo and in vitro trophic actions on central neurotransmitter systems. J. Neurochem. 70, 1335–1345.
Izenwasser, S., Werling, L.L., Cox, B.M., 1990. Comparison of the effects of cocaine and other inhibitors of dopamine uptake in rat striatum, nucleus accumbens, olfactory tubercle, and medial prefrontal cortex. Brain Res. 520, 303–309.
Molina, V.A., Keller, E.A., Orsingher, O.A., 1989. Gangliosides enhance behavioral and neurochemical effects induced by chronic desipramine (DMI) treatment. Eur. J. Pharmacol. 160, 247–252.
O'Brien, C.P., 2001. Drug addiction and drug abuse, In: Hardman, J.G., Limbird, L.E. (Eds.), Goodman & Gilman's "The Pharmacological Basis of Therapeutics", 10th Ed. McGraw-Hill, New York, pp. 621–644.
Perry, J.C., Vital, M.A.B.F., Frussa-Filho, R., Tufik, S., Palermo-Neto, J., 2004. Monosialoganglioside (GM1) attenuates the behavioral effects of long-term haloperidol administration in supersensitive rats. Eur. Neuropsychopharmacol. 14, 127–133.
Rabin, S.j., Bachis, A., Mocchetti, I., 2002. Gangliosides activate TrK receptors by inducing the release of neurotrophins. J. Biol. Chem. 277, 49466–49472.
Rebbaa, A., Portoukalian, J., 1995. Distribution of exogenously added gangliosides in serum proteins depends on the relative affinity of albumin and lipoproteins. J. Lipid Res. 36, 564–572.
Valdomero, A., Isoardi, N.A., Orsingher, O.A., Cuadra, G.R., 2005. Pharmacological reactivity to cocaine in adult rats undernourished at perinatal age: behavioral and neurochemical correlates. Neuropharmacology 48, 538–546.
Valdomero, A., Bussolino, D.F., Orsingher, O.A., Cuadra, G.R., 2006. Perinatal protein malnutrition enhances rewarding cocaine properties in adult rats. Neuroscience 137, 221–229.