Nº PROYECTO : 3110107
TÍTULO PROYECTO : GENE SILENCING OF HCN CHANNELS AND ITS EFFECTS ON THE STIMULATING AND REWARDING EFFECTS OF ETHANOL
DISCIPLINA PRINCIPAL : FARMACOLOGIA
GRUPO DE ESTUDIO : BIOLOGIA 3
INVESTIGADOR(A) RESPONSABLE : MARIO FRANCIS RIVERA MEZA
FECHA: 29/09/2013

FONDO NACIONAL DE DESARROLLO CIENTIFICO Y TECNOLOGICO (FONDECYT)
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INFORME FINAL
PROYECTO FONDECYT POSTDOCTORADO

OBJETIVOS

Cumplimiento de los Objetivos planteados en la etapa final, o pendientes de cumplir. Recuerde que en esta sección debe referirse a objetivos desarrollados, NO listar actividades desarrolladas.

<table>
<thead>
<tr>
<th>Nº</th>
<th>OBJETIVOS</th>
<th>CUMPLIMIENTO</th>
<th>FUNDAMENTO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Intracerebral (stereotaxic) administration of lentiviral vectors</td>
<td>TOTAL</td>
<td>Lentiviral vectors aimed to inhibit or to overexpress the rat HCN2 were generated and administered into the VTA of UChB rats by stereotaxic injection. Proper control lentiviral vectors were also generated and administered.</td>
</tr>
<tr>
<td>2</td>
<td>To determine the effect of VTA HCN2 overexpression on ethanol self-administration</td>
<td>TOTAL</td>
<td>We found that HCN2 overexpression into the VTA of UChB drinking rats results in 2-fold increase in voluntary ethanol intake.</td>
</tr>
<tr>
<td>3</td>
<td>To determine the effect of VTA HCN2 overexpression on the stimulant and rewarding properties of ethanol</td>
<td>TOTAL</td>
<td>We found that overexpression of HCN2 into the VTA of UChB drinking rats results in a remarkable augmentation of the stimulant and reinforcing effects of ethanol. Transduced rats showed an increased conditioned place preference to ethanol, a significant higher locomotor activity and dopamine release in nucleus accumbens upon systemic administration of ethanol.</td>
</tr>
<tr>
<td>4</td>
<td>To determine the effect of VTA HCN2 silencing on ethanol self-administration</td>
<td>TOTAL</td>
<td>We found that HCN2 silencing into the VTA of UChB drinking rats results in 1.5-fold reduction of voluntary ethanol intake.</td>
</tr>
</tbody>
</table>

Otro(s) aspecto(s) que Ud. considere importante(s) en la evaluación del cumplimiento de objetivos planteados en la propuesta original o en las modificaciones autorizadas por los Consejos.

In summary, all the objectives proposed in the original project were completely achieved. Using an in vivo genetic approach we studied whether altering the genetic expression of HCN channels in the VTA of rats affects the addictive effects of ethanol. The experiments attempted to (a) increase the expression of HCN channels into the VTA of UChB rats showed that treated animals increased 2-times their voluntary ethanol intake. Behavioral studies aimed at determining the addictive potential of ethanol (conditioned place preference, locomotor activity, dopamine release) showed that overexpression of HCN channels into the VTA increased the reinforcing and stimulant effects of ethanol. These results generated one manuscript which has been submitted to publication.

The experiments aimed to (b) block the expression of HCN ionic channels in the VTA of UChB rats showed that treated animals reduced 1.5-times their voluntary ethanol intake. It was also found that blocking the expression of HCN channels in animals previously rendered alcohol-dependent resulted in a clear reduction of voluntary ethanol intake. A manuscript based in these results is under preparation.
RESULTS OBTAINED:

A first progress report was submitted and approved by FONDECYT in 2011, demonstrating the complete fulfillment of objectives 1, 2 and 3, including advances for the objectives 4 and 5. A second report was submitted and approved by FONDECYT in 2012, demonstrating the complete fulfillment of objectives 4 and 5, including advances for objectives 6, 7 and 8.

In summary, the main achievements indicated in the reports for 2011 and 2012 were:

**Objective 1: Cloning the rat HCN2 ionic channel cDNA.** The rat HCN2 cDNA was obtained by gene synthesis, confirming its sequence by automatic sequencing. The rHCN2 cDNA was cloned in a plasmid vector, allowing its expression in mammalian cells.

**Objective 2: Determining the rat HCN2 cDNA expression in HEK-293 cells.** Immunofluorescence microscopy, Western blot and electrophysiology assays demonstrated the correct functionality of the cloned rHCN2 cDNA in mammalian cells.

**Objective 3: Design and synthesis of shRNA coding genes to silence rHCN2 expression.** Four complementary short hairpin RNA (shRNA) were generated to block the expression of HCN2 cDNA in cultured cells. The shRNA tested produced a maximum of 50% inhibition of HCN2 expression in cell culture.

**Objective 4: Design and synthesis of siRNA coding genes to silence rHCN2 expression.** Four new small interfering RNA (siRNA) were investigated to improve the results obtained in the inhibition of HCN2 expression in vitro. One of the siRNA generated a 90% inhibition of HCN2 expression.

**Objective 5: Generation of lentiviral vectors.** Lentiviral vectors aimed to overexpress or to inhibit the expression of HCN2 in the VTA of UChB rats were successfully generated.

**Report for the 2013 period.**

The present report concerns objectives 6, 7, 8 and 9 only (see below), since the previous objectives (1, 2, 3, 4 and 5) are considered to be successfully fulfilled.

**Objective 6: Intracerebral (stereotaxic) administration of lentiviral vectors.**

**Objective 7: To determine the effect of VTA HCN2 overexpression on ethanol self-administration.**

**Objective 8: To determine the effect of VTA HCN2 overexpression on the stimulant and rewarding properties of ethanol.**

**Objective 9: To determine the effect of VTA HCN2 silencing on ethanol self-administration.**

**Objective #6: Intracerebral (stereotaxic) administration of lentiviral vectors.**

The aims of objective #6 were: (i) to overexpress the HCN2 gene in the VTA of alcohol-preferring (UChB) rats by intracerebral administration of lentiviral vectors, and (ii) to silence the HCN2 gene in the VTA of UChB rats by intracerebral administration of lentiviral vectors.

In order to study the effects of HCN2 overexpression, we administered $1.5 \times 10^5$ TU/2µL of a lentiviral vector coding for the HCN2 gene plus a GFP reporter (LV-rHCN2-GFP), or a control lentivector (LV-GFP) into the posterior VTA of UChB rats (naive to ethanol consumption) (Rivera-Meza et al., submitted). (See Figure 1).

**Figure 1. Stereotaxic administration of lentiviral vectors into the posterior VTA of rats.** Anesthetized animals were placed in a Kopf stereotaxic frame according to the atlas of Paxinos and Watson (1986). The skull was exposed and via a drilled hole a 2-µL micro-syringe filled with lentiviral vectors was inserted into the left posterior VTA (B-5.6; L-0.5; V-7.4, from Bregma and dura). Two minutes after syringe implantation, 1-2 µL of the corresponding lentiviral vector was infused at the rate of 0.2 µL/min. Thereafter, skin was sutured, and the rat left to recover in a surgery station before being transferred to individual cages at the animal station, with access to water and food ad libitum.
In order to study the effects of HCN2 silencing, we administered $8 \times 10^6$ TU/2 µL of a lentiviral vector coding for a siRNA against rat HCN2 plus a gene coding for GFP reporter (LV-antiHCN2-GFP), or control LV-scramble-GFP lentivirus into the VTA of alcohol-preferring UChB (naïve to ethanol consumption) rats by stereotaxic surgery.

In experiments performed at the laboratory of Dr. Rainer Spanagel (University of Heidelberg, Mannheim, Germany), Wistar rats previously rendered alcohol dependent by a 90-day period of voluntary ethanol intake (5, 10 and 20% three-bottle paradigm) were administered bilaterally into the posterior VTA with $1 \times 10^6$ TU (each side) of the lentiviral vectors LV-antiHCN2-GFP or LV-scramble-GFP control vector.

**Objective #7: To determine the effect of VTA HCN2 overexpression on ethanol self-administration.**

The aim of objective #7 was to determine the effect of overexpressing HCN2 in the VTA of alcohol-preferring (UChB) rats on voluntary ethanol consumption.

Four days after intracerebral administration of the lentiviral vectors, the rats were exposed to a drinking paradigm for 24 hours/day, consisting of free availability to two bottles, one containing 5% (v/v) ethanol and other containing water during 30 days. Ethanol consumption was determined on daily basis and expressed as g ethanol/kg body weight/day. Figure 2 shows that animals receiving a single intracerebral administration of the LV-rHCN2-GFP lentivector significantly increased their voluntary ethanol intake for the tested 30 days period (64% increase, ANOVA $p<0.001$) compared with rats receiving the LV-GFP control lentivector (Rivera-Meza et al., submitted).

![Figure 2. Voluntary ethanol intake of UChB rats administered intracerebrally with a lentivector coding for rHCN2 and GFP.](image)

**Objective #8: To determine the effect of VTA HCN2 overexpression on the stimulant and reinforcing properties of ethanol.**

The aim of objective #8 was to investigate the effect of VTA HCN2 overexpression on the stimulant and reinforcing properties of ethanol, measured as the:

(i) Ethanol-induced conditioned place preference;
(ii) Ethanol-induced locomotion, and
(iii) Ethanol-induced dopamine release in the nucleus accumbens.

(i) Ethanol-induced conditioned place preference. Conditioned place preference (CPP) is a procedure that allows measuring the reinforcing value of a drug. In this assay, the preference towards contextual cues previously paired with a drug is evaluated by measuring the time spent in a place where a drug has been previously administered. Figure 3 shows that rats treated with
LV-rHCN2-GFP or LV-GFP lentivectors did not show significant differences in the time spent in the less preferred box before conditioning (21.28 ± 4.08 vs 18.98 ± 3.56 % of time; t-test: t=-2.3, df=16, p=0.34, white bars). On alternate days, animals received five conditioning sessions on which ethanol (0.5 g/kg, i.p.) was administered and placed in the less preferred compartment for 15 min. Post-conditioning session showed that rats treated with the LV-rHCN2-GFP vector developed a marked CPP to the ethanol-paired box, expressed as a ~3-fold increase of the time spent in the ethanol paired-box compared to pre-conditioning value (53.83 ± 7.84 versus 18.98 ± 3.56 % of time; t-test: t=-4.05, df=16, p<0.001). The post-conditioning time spent in the ethanol-paired box by control rats (LV-GFP) showed a slight, but non-significant CPP (32.20 ± 6.06 versus 21.28 ± 4.08 % of time; t-test: t=-1.49, df=16, p=0.07) (Rivera-Meza et al., submitted).

Figure 3. HCN2 overexpression increases the development of ethanol-induced conditioned place preference in UChB rats. The CPP assay was performed in rectangular boxes with two-end compartments (one, black walls smooth floor; and the other, white walls-gridded floor) and a middle passageway (gray walls-smooth floor). A first pre-conditioning session was conducted for assessing unconditioned chamber preference. During the conditioning phase, guillotine doors were closed so that the rats were confined to one side of the apparatus. During 10 days rats were administered with ethanol (0.5 g/kg, i.p.) and 10 min later placed in the less preferred compartment for 15 min. On alternate days, the rats were administered saline and placed in the preferred compartment. The post-conditioning phase started 24 hours after the last conditioning trial. The post-conditioning phase consisted in a 15-min choice test with no injection, while the rats freely moved through the passageway between the two chambers. The time spent by each rat in each compartment was recorded during 15 min trials. Data are expressed as the percentage of total time spent in the ethanol-paired chamber.

(ii) Ethanol-induced locomotion. Figure 4 shows the ethanol- (0.5 g/kg, i.p.) or saline-induced locomotor activity (three successive five-minute intervals after administration of ethanol or saline) of rats treated with LV-rHCN2-GFP or LV-GFP lentivectors. Rats treated with the control vector LV-GFP did not show any change in locomotor activity after ethanol administration (Figure 4A). Figure 4B shows the results obtained in rats treated with LV-rHCN2-GFP vector. A dose of ethanol induced a significant increase in locomotor activity during the first 5-minute interval, compared to that produced by saline administration (47.9 ± 5.1 versus 31.0 ± 3.9 AU; t-test: t=7.01, df=8, p<0.001). No significant differences in locomotor activity were observed in the subsequent second and third 5-minute intervals (Rivera-Meza et al., submitted).

(iii) Ethanol-induced dopamine release in nucleus accumbens. The marked increase in the reinforcing and stimulating effects of ethanol showed by the animals treated with LV-rHCN2-GFP vector prompted us to determine if such effect had a parallel increase in nucleus accumbens (NAcc) dopamine release induced by systemic ethanol administration. Figure 5 shows the extracellular levels of dopamine in NAcc (% of basal levels) elicited by the administration of ethanol (1 g/kg, i.p.) in rats treated with LV-rHCN2-GFP or LV-GFP lentivectors. Animals treated with the control vector did not show any significant increase of dopamine levels in the NAcc after ethanol administration compared to basal condition (100.1 ± 10.2 versus 106.6 ± 12.3 % of base-line; t-test: t=-0.36, df=4, p=0.36). Acute ethanol administration to animals treated with LV-rHCN2-GFP elicited a ~2-fold increase of NAcc dopamine levels compared to the basal condition (100.0 ± 14.3 versus 160.2 ± 21.8 % of base-line; t-test: t=-2.58, df=3, p<0.05) (Rivera-Meza et al., submitted)
Figure 4. HCN2 overexpression increases ethanol-induced locomotor activity in UChB rats. The open-field apparatus consisted of a chamber (38 x 38 x 38 cm) painted black and floor marked with lines each 9.5 cm forming a 4 x 4 grid. Animals received three daily 15 minutes habituation sessions, prior to drug tests. In the first test session, rats treated with the lentivectors LV-rHCN2-GFP or LV-GFP were administered a dose of 0.5 g ethanol/kg (i.p.) and 10 min later each rat was individually placed in the center of the open-field for recording horizontal locomotion for 15 minutes. An activity unit (AU) represents the complete crossing from one square to another. Twenty-four hours later, a second session was performed using saline as treatment.

Figure 5. HCN2 overexpression in the VTA increases ethanol-induced release of dopamine in the NAcc of UChB rats. Approximately two months after the intracerebral administration of the lentiviral vectors, animals were anesthetized and placed in a Kopf stereotaxic frame with the skull oriented according to the atlas of Paxinos and Watson (1986). The rats were implanted with a microdialysis probe (dialysis length, 2mm; diameter, 0.6 mm; cut off, 6kD) into the left nucleus accumbens (A 1.7, L-0.7, V-8.2). Microdialysis probes were connected to a perfusion pump, and perfused with a Ringer solution (pH~7) at a flow rate of 2µl/min. Samples (60 µl) were collected every 30 min and assayed for dopamine by HPLC coupled to electrochemical detection. The identification and quantification of the substances was achieved by comparison with standard solutions prepared similarly to the samples. Immediately after baseline sampling (four 30-min samples), rats were treated with 20% (v/v) ethanol (in saline), to give a dose of 1.0 g of ethanol/kg body weight (i.p.). Three additional 30-min samples were collected and analyzed for dopamine as described above.

Objective #9: To determine the effect of VTA HCN2 silencing on ethanol self-administration.

The aim of objective #9 was to determine the effect of silencing HCN2 expression in the VTA of rats on voluntary ethanol consumption.

(i) HCN2 silencing in UChB rats (naive to alcohol): Four days after intracerebral administration of the lentiviral vectors (LV-antiHCN2-GFP or LV-scramble-GFP), the animals were exposed to a drinking paradigm for 24 hours/day, consisting of free availability to two bottles, one containing 10% (v/v) ethanol and other containing water during 15 days. Ethanol consumption was determined on daily basis and expressed as g ethanol/kg/day ± SEM. Figure 6 shows that animals receiving a single intracerebral administration of the LV-antiHCN2-GFP lentivector showed
a significant decrease of their voluntary ethanol intake for the tested 15 days period compared with rats receiving the LV-scramble-GFP control lentivirus (two-way ANOVA for treatment, $F_{(1,29)}=34.54; p<0.001$). The main daily ethanol consumption in the LV-antiHCN2-GFP group was $\sim 1.5$ lower compared to the LV-scramble-GFP group ($3.75 \pm 0.16$ vs. $5.87 \pm 0.15$ g ethanol/kg/day; t-test, $t=0.525$, $df=28$, $p<0.001$) (Manuscript in preparation).

**Figure 6. Voluntary ethanol intake of UChB rats administered intracerebrally with a lentivirus aimed at inhibiting HCN2 expression.** Naïve UChB rats were assigned to two groups. One group was administered with $8 \times 10^6$ TU/2 µL of the lentiviral vector LV-antiHCN2-GFP ($n=10$) into the posterior VTA, and the other with LV-scramble-GFP control vector ($n=7$). Ninety-six hours after the administration of the lentiviral vectors, access to 10% ethanol and water was allowed for 15 days. Points represent means ± SEM of daily ethanol intake. Rats treated with LV-antiHCN2-GFP showed a significant reduction of voluntary ethanol intake, compared with control animals [ANOVA; $F_{(1, 29)}=34.54, P<0.001$].

**(ii) HCN2 silencing in alcohol dependent rats:** These experiments were performed at the laboratory of Dr. Rainer Spanagel (University of Heidelberg, Mannheim, Germany). Twenty Wistar rats (non selected for ethanol consumption) were rendered alcohol dependent by a 90-day period of voluntary ethanol intake consisting in a 24-hours free availability paradigm between water and three solutions of alcohol of different concentration (5, 10 and 20%). After this period, alcohol access was suppressed for two weeks to generate an alcohol deprivation effect in the animals. At the third day of deprivation the animals were divided into two groups and administered bilaterally into the posterior VTA with $1 \times 10^6$ TU (each side) of the lentiviral vectors LV-antiHCN2-GFP or LV-scramble-GFP control vector. After the 2-week deprivation period, alcohol access was reinstated for two weeks to generate an alcohol deprivation effect in the animals. At the third day of deprivation the animals were divided into two groups and administered bilaterally into the posterior VTA with $1 \times 10^6$ TU (each side) of the lentiviral vectors LV-antiHCN2-GFP or LV-scramble-GFP control vector. After the 2-week deprivation period, alcohol access was reinstated and ethanol consumption determined on a daily basis and expressed as g ethanol/kg/day ± SEM. Figure 7 shows that animals receiving the intracerebral administration of the LV-antiHCN2-GFP lentivirus showed a clear statistically significant decrease of their voluntary ethanol intake for the first 3 days post-deprivation period compared with rats receiving the LV-scramble-GFP control lentivirus (two-way ANOVA for treatment days 1-3, $F_{(1,56)}=5.89; P<0.01$).

**Figure 7. Ethanol intake before and after an alcohol deprivation period in rats treated with the lentivirus aimed at inhibiting HCN2 expression.** Either LV-scramble-GFP control vector or LV-antiHCN2-GFP vector were administered during the first 3 days of abstinence. The last week measurements of ethanol intake are given as baseline drinking “B”. Data are presented as g ethanol/kg/day ± S.E.M. $P<0.01$ for comparison AUC (days 1-3) (LV-scramble-GFP versus LV-antiHCN2-GFP)

2. The paper entitled "Gene specific modifications unravel ethanol and acetaldehyde actions" by Yedy Israel, Mario Rivera-Meza, Eduardo Karahanian, María Elena Quintanilla, Lutske Tampier, Paola Morales and Mario Herrera-Marschitz was published in Frontiers in Behavioral Neuroscience Journal (Front Behav Neurosci 7:80, 2013). This paper is a product of a fundamental collaboration with Drs. Yedy Israel and Mario Herrera-Marschitz framework. See article in Annex 1.

3. The manuscript entitled "Marked inhibition of alcohol reinforcement and binge drinking by administration of the aldehyde dehydrogenase (ALDH2) gene into the ventral tegmental area" by Eduardo Karahanian, Mario Rivera-Meza, Lutske Tampier, María Elena Quintanilla, Mario Herrera-Marschitz and Yedy Israel, has been submitted to Addiction Biology Journal. This manuscript is a result of the collaboration with Drs. Yedy Israel and Mario Herrera-Marschitz framework. See the manuscript in Annex 1.

4. I visited the Department of Psychopharmacology, Central Institute of Mental Health, University of Heidelberg, Mannheim, Germany; led by Dr. Rainer Spanagel during October 16th to December 16th, 2012. Please see Report of International Visit in Annex 2.

5. During the present academic year (2013), I have supervised two Experimental Research Unit of medicine students.
Mr. Yanggang Gong and Mr. Matías Garrido on a project entitled "Expresión del canal HCN-2 en el sistema meso-cortico-límbico de ratas no bebedoras (UChA) y bebedoras (UChB): Efecto del alcohol sobre su expresión”. See the project in Annex 2.
Mr. Diego Alonso, Mr. Diego Alvarez and Mr. Tomás Aguirre on a project entitled "Evaluación del fenotipo depresivo en ratas bebedoras (UChB) y no bebedoras de alcohol (UChA)”. See the project in Annex 2.
I have co-supervised the Experimental Thesis of Freddy Valdivia (Medical Technology student) on a project entitled "Síntesis de isosalsolinol y su purificación por HPLC preparativo para estudiar su efecto sobre el consumo de alcohol en ratas”. See the project in Annex 2.

6. I am participating in the FONDECYT initiative “1000 científicos, 1000 aulas”, to take place in the schools "Nuestra Señora de Andacollo” (Santiago, Santiago) and “Boston College” (La Florida, Santiago) in October 10th, 2013. I will give a lecture entitled “El alcohol: que es y cuáles son sus efectos” that is orientated to high-school level students, aimed to explain the biological bases of alcohol dependence and its consequences for the human physiology.

7. I participate as co-coordinator at the IV International Diploma on Neuropsychopharmacology (MEDICHI, Chile) addressing candidates to psychiatry, neurology and neuropediatrics.

8. I participate as invited teacher at the postgraduate course Molecular Biology & Gene Therapy (Faculty of Chemical and Pharmaceutical Sciences, University of Chile) orientated to health and biomedical professionals.
I was pleased when sponsoring the postdoc project by Dr. Mario Rivera-Meza (FONDECYT-Postdoctoral project No 3110107, entitled *Gene silencing of HCN channels and its effects on the stimulating and rewarding effects of ethanol*, but particularly now when evaluating the final outcome of project.

Two full papers are under evaluation in leading journals of the field (Addiction Biology, Alcoholism Clin Exp Res) reporting the main outcomes of the project, apart of two already published papers for which the results obtained in the project have played a fundamental role for designing a strategy for dealing with alcoholism. The project also led to several communications for international conferences, in Europe and America, and provided a framework for a FONDECYT-Initiation project (#1130154, under evaluation), and an already financed Regular project (#1130012; Quintanilla et al).

The project demonstrated that HCN ionic channels represent an important cellular mechanism mediating the *in vivo* pharmacological effects of ethanol, in particular those channels localized in VTA, a brain region containing the dopamine cell bodies projecting to mesolimbic and mesocortical areas, known to be involved in the neurochemical mechanisms of addiction. The project predicts the development of HCN blockers able to cross the blood brain barrier, providing a novel strategy for treating alcohol addiction.

The project developed several cutting-edge molecular technologies for generating biological carriers, modifying the genome of addicted rats, evaluated *in vitro* and *in vivo*, in particular using UChB rats, a paradigm for studying alcoholism established by pioneering studies carried out in Chile during fifties by Prof. Jorge Mardones Restat.

The work of Dr. Mario Rivera Meza has also being pivotal for developing several molecular biology techniques developed in our own lab, financed by FONDECYT (#1120079; #1110263), Millenium Initiative (BNI P09-015-F) and other international grants. Dr. Rivera participates as a senior researcher, supervising undergraduate and graduate students, and further scientific initiatives, certainly representing a renewal for the future of our institution.

Sponsor signature

Professor Mario Herrera-Marschitz, MD Sci PhD; Date: Santiago, September 27, 2013
PRODUCTOS

ARTÍCULOS
Para trabajos en Prensa/ Aceptados/Enviados adjunte copia de carta de aceptación o de recepción.

N° : 1
Autor (a)(es/as) : Israel, Y.; Rivera-Meza M.; Karahanian, E.; Quintanilla, ME.; Tampier, L.; Morales, P.; Herrera-Marschitz, M.
Nombre Completo de la Revista : Frontiers in Behavioral Neuroscience
Título (Idioma original) : Gene specific modifications unravel ethanol and acetaldehyde actions
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N° : 2
Autor (a)(es/as) : Karahanian, E.; Rivera-Meza, M.; Tampier, L.; Quintanilla, ME.; Herrera-Marschitz, M; Israel, Y.
Nombre Completo de la Revista : Addiction Biology
Título (Idioma original) : Marked inhibition of alcohol reinforcement and binge drinking by administration of the aldehyde dehydrogenase (ALDH2) gene into the ventral tegmental area
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Nº : 3
Autor (a)(es/as) : Rivera-Meza, M.; Quintanilla, ME.; Bustamante, D.; Delgado, R.; Buscaglia, M.; Herrera-Marschitz, M.
Nombre Completo de la Revista : Alcoholism: Clinical and Experimental Research
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Sin información ingresada.

CONGRESOS

Nº : 1
Autor (a)(es/as) : Berríos-Cárcamo, P.; Quintanilla, ME.; Rivera-Meza, M.; Buscaglia, M.; Zapata-Torres, G.; Herrera-Marschitz, M.; Israel, Y.
Título (Idioma original) : Salsolinol and isosalsolinol: products of dopamine and acetaldehyde condensation as putative effectors of the reinforcing effects of ethanol
Nombre del Congreso : II International Workshop. Motivated Behaviors, Stress and Addiction: From molecules to behavior
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Título (Idioma original) : Is salsolinol the final effector for ethanol reinforcement?
Nombre del Congreso : VI Neurotoxicity Society Meeting
País : CHILE
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Autor (a)(es/as) : Rivera-Meza, M.; Quintanilla, ME.; Tampier, L.; Herrera-Marschitz, M.
Título (Idioma original) : HCN-2 ionic cannel is relevant for the rewarding and stimulant properties of ethanol
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Ciudad : Valdivia
Fecha Inicio : 21/03/2013
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Overexpression of HCN channels into the ventral tegmental area increases the rewarding effects of ethanol

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Orlando
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Alcoholism: Clinical and Experimental Research
2013
37
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59A
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El alcohol es metabolizado en un producto aversivo en el hígado, pero adictivo en el cerebro: implicaciones terapéuticas
Encuentro ICBM 2013: Aportes del ICBM a las Ciencias Biomédicas
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