I CUMBRE
CELAC
Chile | 2013

SIMPOSIO "AVANCES Y DESAFÍOS EN LA INVESTIGACIÓN CIENTÍFICA SOBRE TRATAMIENTOS, ESTRATEGIAS FARMACOLÓGICAS Y VACUNAS CONTRA LA ADICCIÓN A LAS DROGAS"

12 al 14 de Noviembre de 2012 | Hotel Atton Vitacura | Santiago de Chile

SYMPOSIUM "PROGRESS AND CHALLENGES IN SCIENTIFIC RESEARCH ON TREATMENTS, PHARMACOLOGICAL STRATEGIES AND VACCINES AGAINST DRUG ADDICTION"

12 -14 November 2012 | Hotel Atton Vitacura | Santiago, Chile

"Pre-clinical study of brain effects induced by Coca-Paste"

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Instituto de Investigaciones Biológicas "Clemente Estable"
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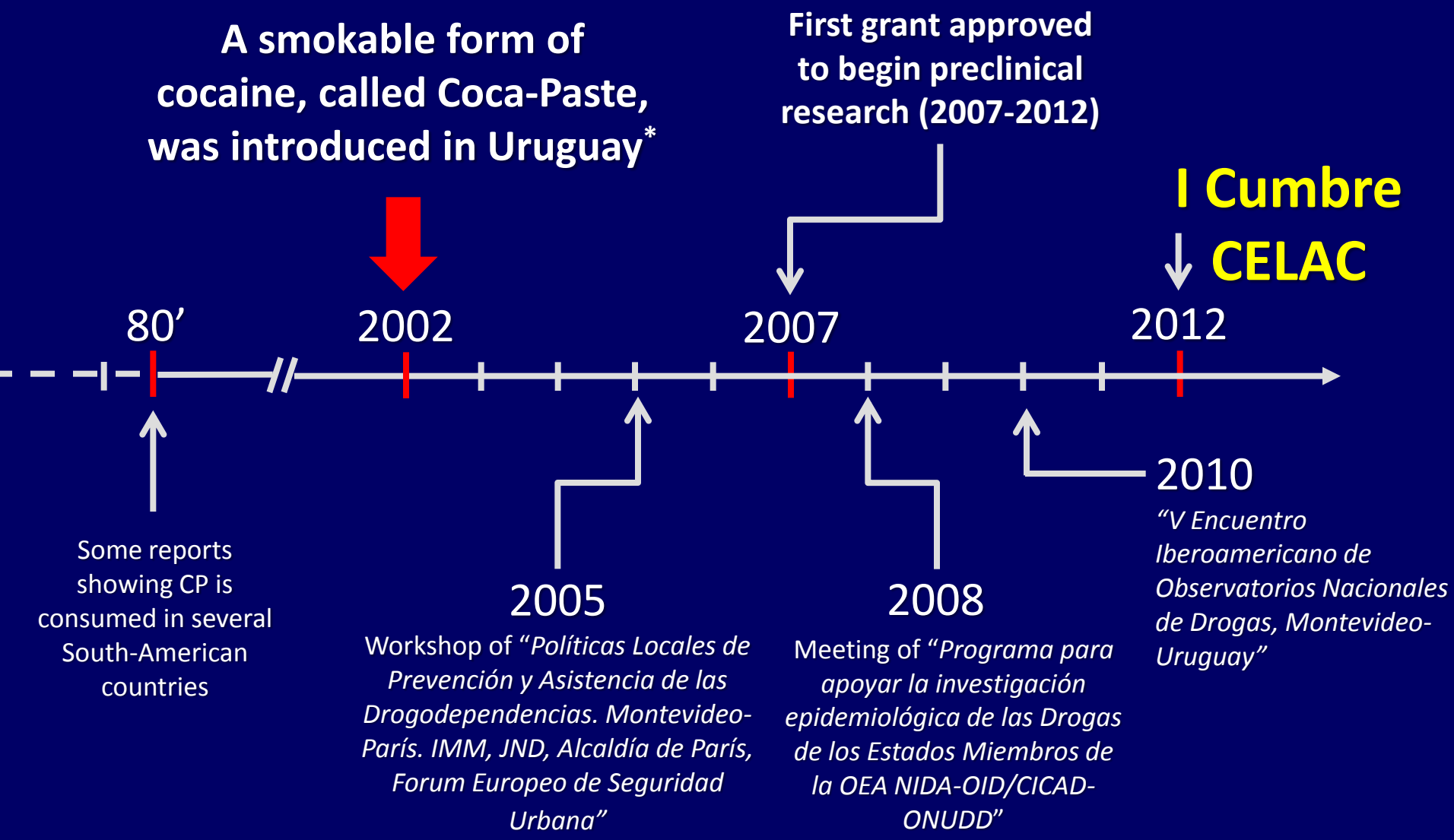
Overview

- Background of Coca-Paste
- Clinical profile of CP-consumers
- Hypothesis and Aims
- Results
- Future directions and questions

Background of CP



Initial questions …

- **What is Coca-Paste?**
- **Is it a new drug of abuse in Latin America?**
- **Is there any information about CP neurobiological actions?**
- **Although it is a smokable form of cocaine, is it different to sniffed cocaine?**
- **Can CP effects be explained only by the route of administration?**

Background of CP: definition

Low prevalence (1 %) respect to other legal or illicit drugs but increases in low income zones (8 %). Health and social public troubles.

National Board of Drugs Survey 2012

Erythroxylon coca bush ➡ **Coca-Paste** ➡ **Cocaine hydrochloride** ➡ **Crack**

- earliest intermediate product obtained during any of the preliminary phases of cocaine alkaloid extraction;

- **cocaine base** as main alkaloid (likewise crack);

- other chemical substances called **impurities** (substances present in the drug as a natural result of the manufacturing process);

- **adulterants**: CP is sold adulterated (subtances deliberately added to improve or mimic the effect of the drug; diluents to increase volume).

Castagno 2000; Lizasoain et al. 2002; López Hill et al. 2011

- **Its consumption follows 4 steps:**

1) EUPHORIA: very high and fast hyperstimulation, disinhibition, pleasure.

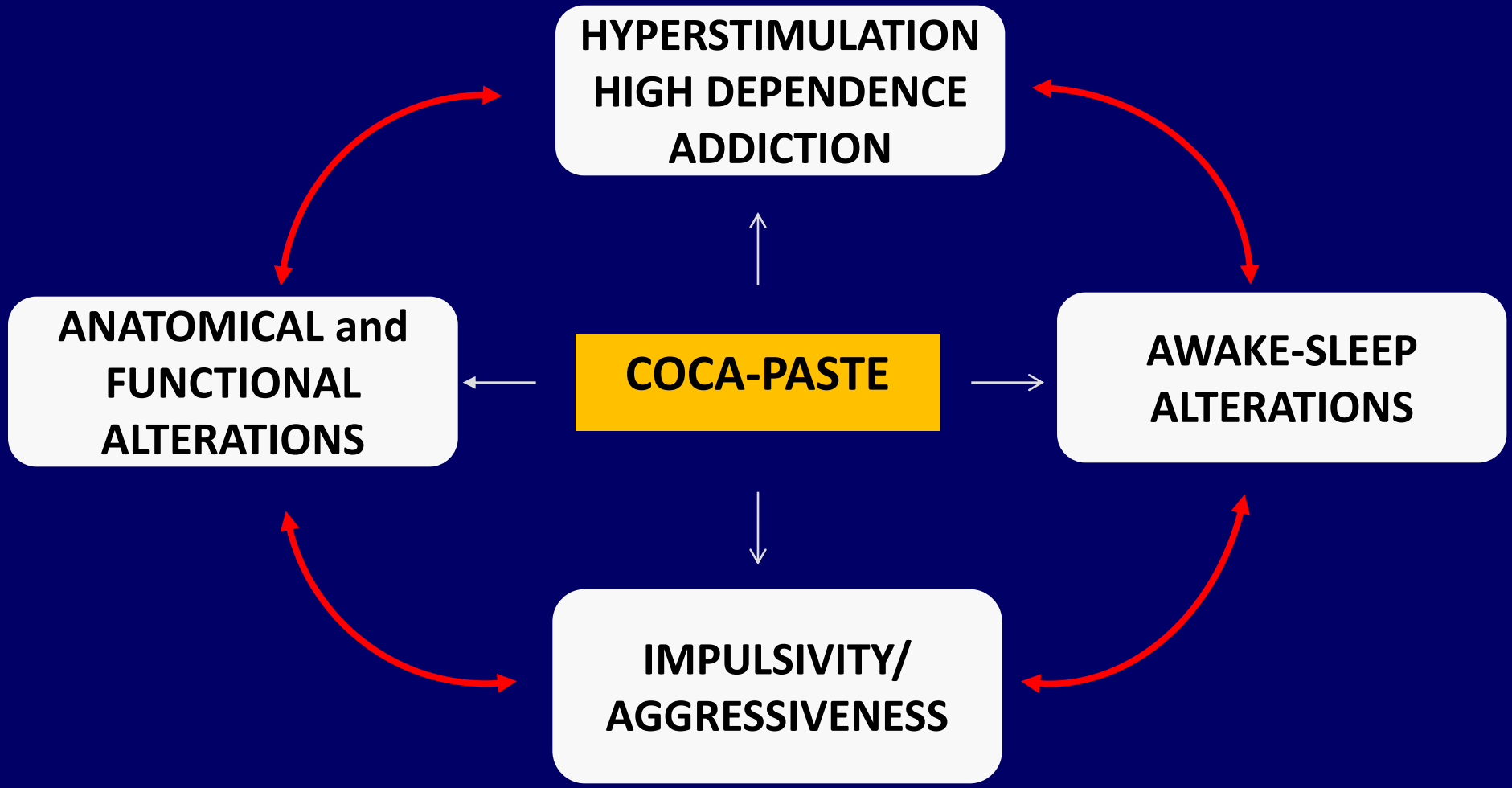
2) DISPHORIA: depressed mood, unhappiness, apathy. High desire to continue smoking

3) CONTINOUS CONSUMPTIONS: mainly to avoid disphoria

4) PSYCHOSIS AND HALLUCINATIONS

National Board of Drugs 2006

• Clinical Profile of CP consumers



Ferrando et al. 2009: Triaca et al. 2009; Pascale et al. 2010; Castagno 2000; Lizasoain et al. 2002.

I.I.B.C.E.

Although the biological and psychological effects of Coca-Paste and cocaine (hydrochloride) are similar…

Route of administration

Coca-Paste	**vs.**	**Cocaine hydrochloride**
Can be easily smoked, vaporizing at a lower temperature; is rapidly absorbed into the blood. Rapid absorption of cocaine through the lungs, because of the large surface area of the alveoli and small airways.		Cannot be smoked because it is decomposed at temperatures required to volatilization. Cocaine is sniffed or i.v injected

I.I.B.C.E.

Relevance of the route of administration

The speed at which drug of abuse enter the brain has been recognized as a key parameter affecting its stimulant and reinforcing effects; increases the propensity to addiction

Samaha and Robinson 2005; Volkow et al. PNAS, 2010

… “smoked cocaine (‘crack’) is thought to be more addictive than powdered cocaine taken by insufflation”

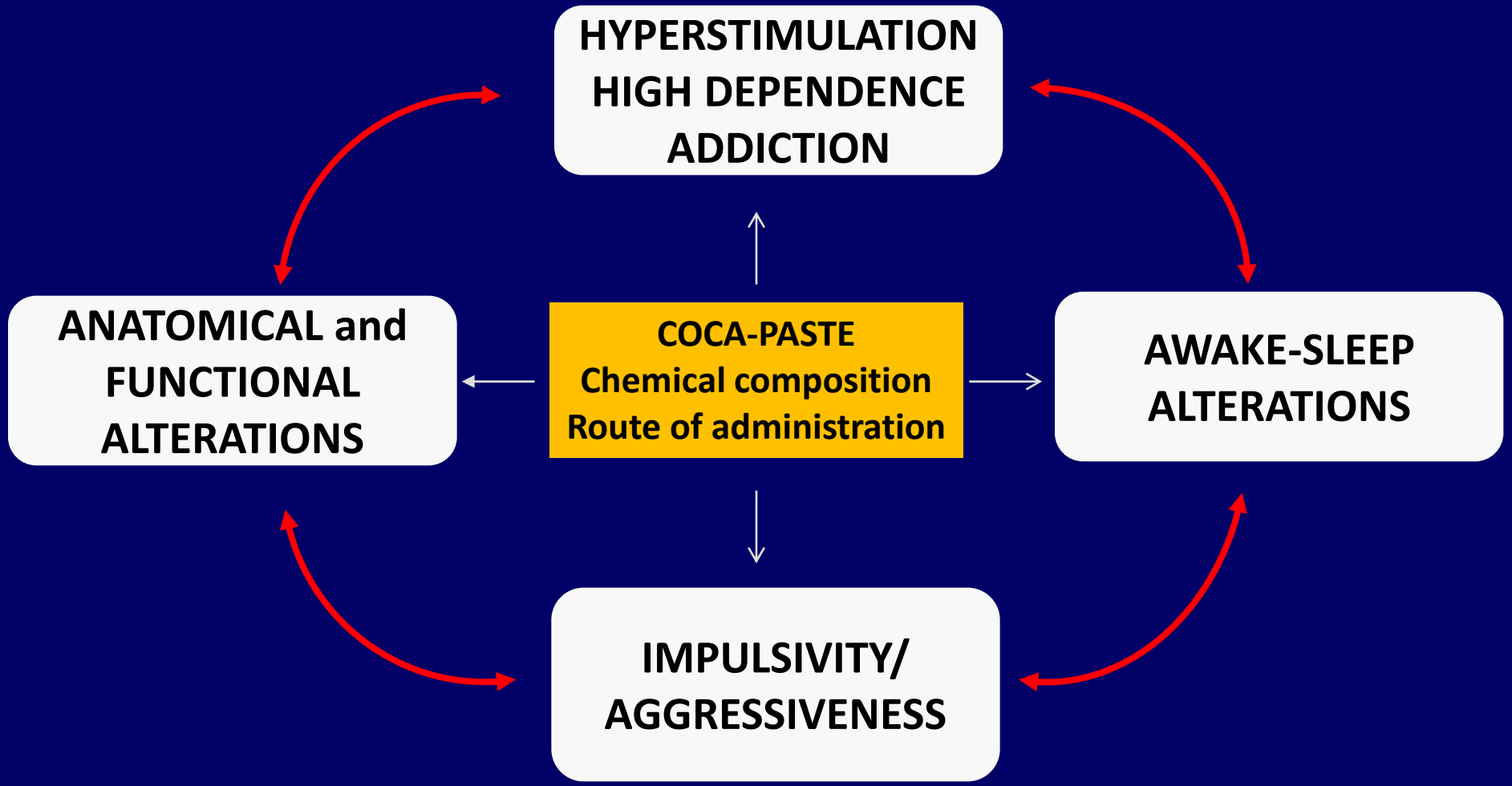
Hatsukami and Fischman, 1996

HYPOTHESIS

Cocaine + impurities + adulterants

It would be relevant to consider the CP chemical composition to explain its neurobiological actions

MAIN GOAL: To study the role of CP chemical composition and route of administration in the clinical profile of consumers



SPECIFIC AIMS

1. **To perform a chemical analysis of CP samples**
2. **To study the role of cocaine + impurities + adulterants in the CP-induced behavioral response (stimulant effect)**
3. **To study CP-induced behavioral response (stimulant effect) reproducing the route of administration of CP-users.**

SPECIFIC AIMS

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CP seized samples

Legal mechanism:Technical Forensic Institute (Montevideo-Uruguay) and National Drugs Board permissions.

Are samples that could be possibly consumed by drug users

RESULTS I: *chemical composition of CP samples from Uruguay*

	Alkaloids			MAIN adulterant*
Samples	COCAINE (base)	TRANS-CINAMOIL Cocaine	CIS-CINAMOIL Cocaine	CAFFEINE
CP 1	67.8 ± 3.6	1.8 ± 0.2	0.6 ± 0.2	15.0 ± 0.3
CP 2	67.4 ± 1.2	4.2 ± 0.2	1.9 ± 0.2	14.0 ± 0.2
CP 3	59.3 ± 0.6	0.9 ± 0.2	0.4 ± 0.2	14.0 ± 0.1
CP 4	59.9 ± 4.5	1.0 ± 0.2	1.4 ± 0.2	13.0 ± 0.5
CP 5	50.2 ± 1.0	nd	nd	1.0 ± 0.5
CP 6	68.2 ± 2.0	nd	nd	1.0 ± 0.1
CP 7	20.7 ± 1.0	nd	nd	10.0 ± 0.2
Cocaine	89.6 ± 0.0	-	-	-
Caffeine		-	-	100 ± 0.0

*Anfetamine; lidocaine; xilasine

nd: non determined

RESULTS I: *chemical composition of CP samples from Uruguay: three categories*

	Alkaloids			MAIN adulterant*
Samples	COCAINE (base)	TRANS-CINAMOIL Cocaine	CIS-CINAMOIL Cocaine	CAFFEINE
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CP 2	67.4 ± 1.2	4.2 ± 0.2	1.9 ± 0.2	14.0 ± 0.2
CP 3	59.3 ± 0.6	0.9 ± 0.2	0.4 ± 0.2	14.0 ± 0.1
CP 4	59.9 ± 4.5	1.0 ± 0.2	1.4 ± 0.2	13.0 ± 0.5
CP 5	50.2 ± 1.0	nd	nd	1.0 ± 0.5
CP 6	68.2 ± 2.0	nd	nd	1.0 ± 0.1
CP 7	20.7 ± 1.0	nd	nd	10.0 ± 0.2
Cocaine	89.6 ± 0.0	-	-	-
Caffeine		-	-	100 ± 0.0

*Anfetamine; lidocaine; xilasine

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CP 3	59.3 ± 0.6	0.9 ± 0.2	0.4 ± 0.2	14.0 ± 0.1
CP 4	59.9 ± 4.5	1.0 ± 0.2	1.4 ± 0.2	13.0 ± 0.5
CP 5	50.2 ± 1.0	nd	nd	1.0 ± 0.5
CP 6	68.2 ± 2.0	nd	nd	1.0 ± 0.1
CP 7	20.7 ± 1.0	nd	nd	10.0 ± 0.2
Cocaine	89.6 ± 0.0	-	-	-
Caffeine		-	-	100 ± 0.0

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CP 3	59.3 ± 0.6	0.9 ± 0.2	0.4 ± 0.2	14.0 ± 0.1
CP 4	59.9 ± 4.5	1.0 ± 0.2	1.4 ± 0.2	13.0 ± 0.5
CP 5	50.2 ± 1.0	nd	nd	1.0 ± 0.5
CP 6	68.2 ± 2.0	nd	nd	1.0 ± 0.1
CP 7	20.7 ± 1.0	nd	nd	10.0 ± 0.2
Cocaine	89.6 ± 0.0	-	-	-
Caffeine		-	-	100 ± 0.0

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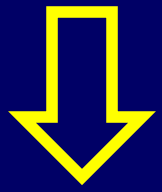
Coca-Paste

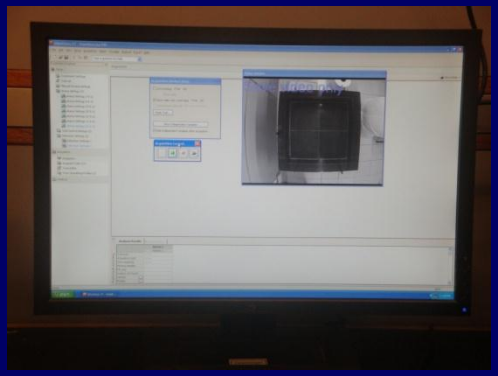


COCAINE

OTHER COMPOUNDS

• ACUTE STIMULANT EFFECT

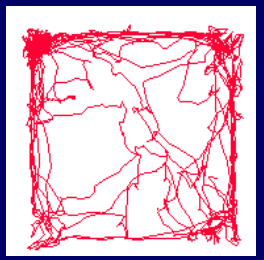
CP or Cocaine
(equivalents doses of cocaine base i.p.)



Open field Paradigm
+ Ethovision XP 7.0

3 categories:

Sample	Cocaine	Caffeine
CP 1	68.9	15.0
CP 5	68.2	1.0
CP 7	20.7	10.3

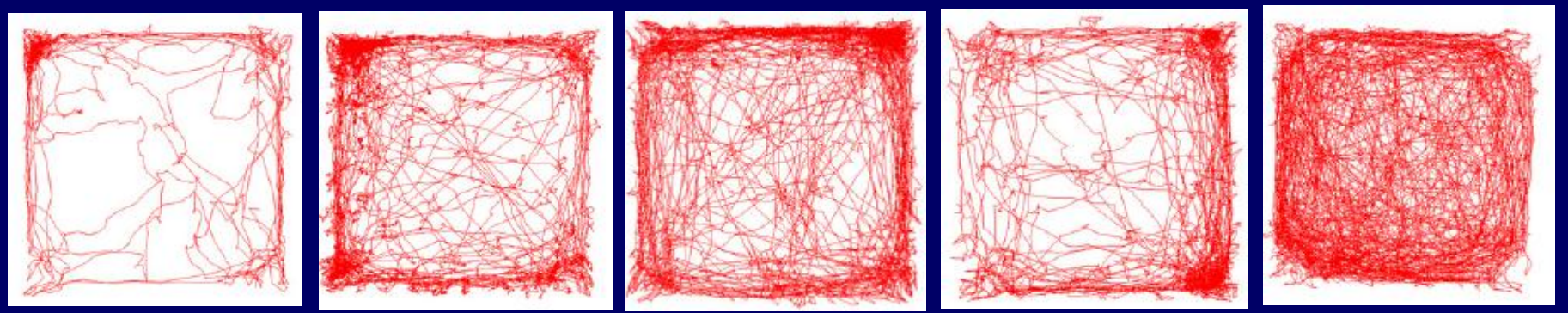


tracking

To measured the stimulant effect → Pattern of movement and distance moved (m)

RESULTS II: *Stimulant effect induced by CP1, CP 5, CP 7 and Cocaine (acute)*

DIFFERENTIAL PATTERN of MOVEMENT



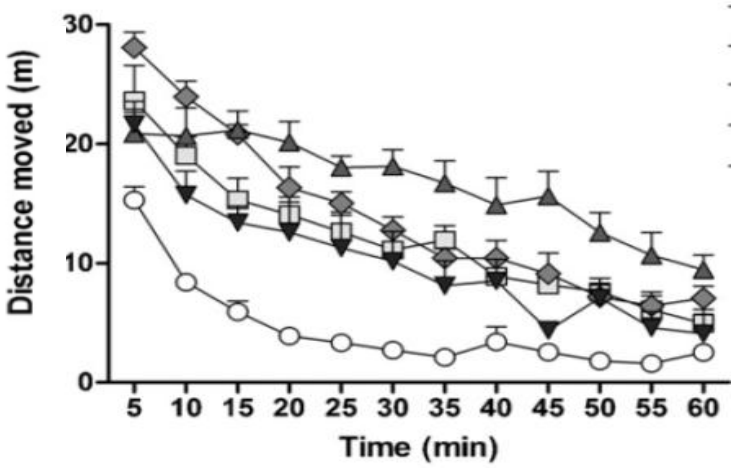
control | Cocaine (5) | CP 1 (5) | CP 5 (5) | CP 7 (5)

Similar effect but different from CP 7

Sample	Cocaine	Caffeine
CP 1	68.9	15.0
CP 5	68.2	1.0
CP 7	20.7	10.3

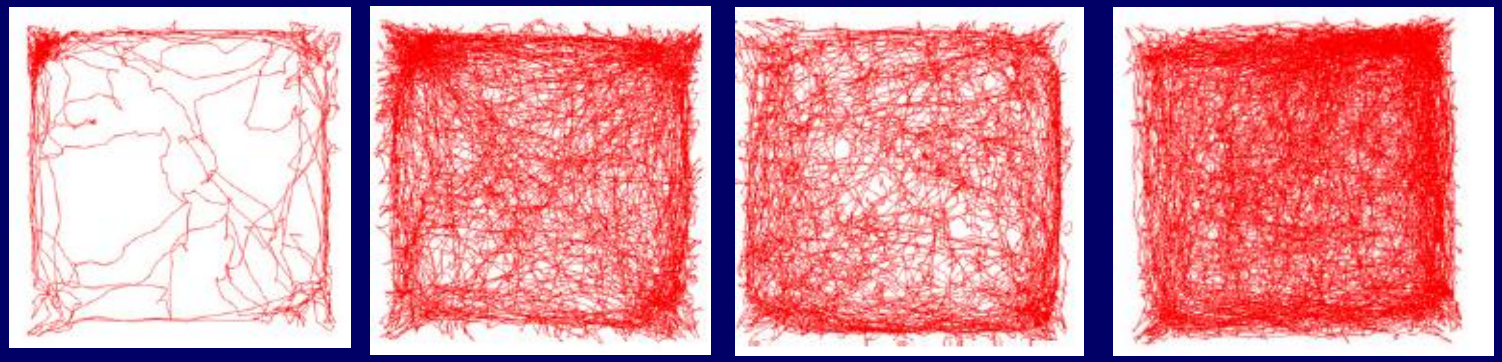
RESULTS II: *Stimulant effect induced by CP1, CP 5, CP 7 and Cocaine (acute)*

Treatment	Mean ± SEM of distance moved (m)
Control	55.6 ± 4.3
Cocaine (5)	143.4 ± 11.1***
CP 1 (5)	167.6 ± 9.1***
CP 5 (5)	133.9 ± 11.8***
CP 7 (5)	198.9 ± 16.4***++//



RESULTS II: *Stimulant effect induced by CP1, CP 5 and Cocaine (acute)*

DIFFERENTIAL PATTERN of MOVEMENT



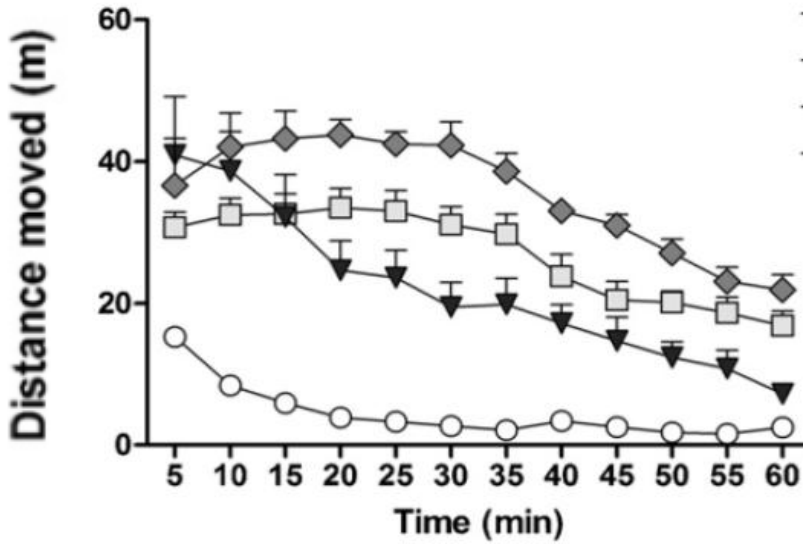
control Cocaine (20) CP 5 (20) CP 1 (20)

Similar effect but different from CP 1

Sample	Cocaine	Caffeine
CP 1	68.9	15.0
CP 5	68.2	1.0
CP 7	20.7	10.3

RESULTS II: *Stimulant effect induced by CP1, CP 5 and Cocaine (acute)*

Treatment	Mean ± SEM of distance moved (m)
Cocaine (20)	$323.0 \pm 25.8^{***}$
CP 1 (20)	$425.2 \pm 22.2^{***++///}$
CP 5 (20)	$261.6 \pm 38.2^{***}$

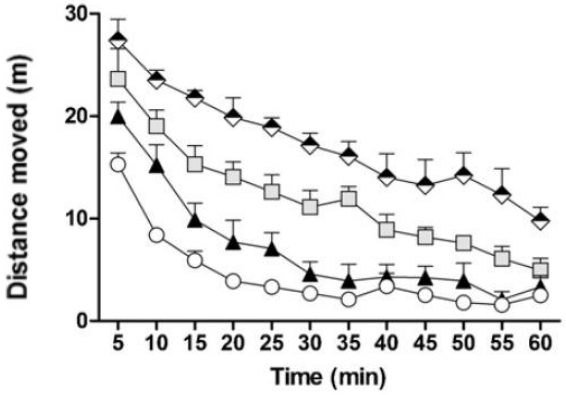


Doses of caffeine calculated based on cocaine and caffeine contents of three CP samples assayed.

CP samples	Doses of cocaine (mg/kg)	Doses of caffeine (mg/kg)
CP 1	5	1.1
	20	4.5
CP 5	5	0.07
	20	0.3
CP 7	5	2.5

Table shows the doses of caffeine calculated based on the cocaine doses at which CP samples were injected.

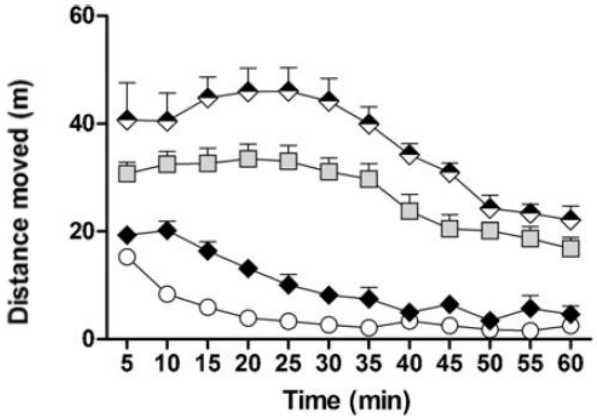
RESULTS II: *Surrogates of CP 1 and CP 7*



Simile to CP 7 (5)

Treatment	Mean ± SEM of distance moved (m)
Control	55.6 ± 4.3
Cocaine (5)	143.4 ± 11.1***
Coc (5) + Caf (2.5)	191.3 ± 19.1***++###
Caffeine (2.5)	86.2 ± 10.9++

CP 7 (5)= 198.9 ± 16.4



Simile to CP 1 (20)

Treatment	Mean ± SEM of distance moved (m)
Control	55.6 ± 4.3
Cocaine (20)	323.0 ± 25.8***
Coc (20) + Caf (4.5)	414.9 ± 38.4***+###
Caffeine (4.5)	119.9 ± 9.1+++

CP 1 (20)= 425.2 ± 22.2

Coca-Paste

COCAINE

OTHER COMPOUNDS

It is one of the responsible compounds for the CP-stimulant effect, but caffeine also contributes;

… they act in an additive fashion when achieved specific proportions;

… impurities do not participate

Caffeine was not detected in all analyzed CP samples

Rev Psiquiatr Urug 2009;73(1):25-36

Primer estudio pre-clínico de la acción de pasta base de cocaína en el sistema nervioso central

Trabajos originales

María Noel Meikle Ximena López Hill Jessika Urbanavicius Eleuterio Umpiérrez Juan Andrés Abín· Carriquiry Giselle Prunell María Cecilia Scorza

Behavioural Brain Research 221 (2011) 134–141

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Coca-paste seized samples characterization: Chemical analysis, stimulating effect in rats and relevance of caffeine as a major adulterant

Ximena López-Hill[a,1], José Pedro Prieto[a,1], María Noel Meikle[a], Jessika Urbanavicius[a], Juan Andrés Abin-Carriquiry[b], Giselle Prunell[b], Eleuterio Umpiérrez[c], María Cecilia Scorza[a,*]

Rev Psiquiatr Urug 2012;76(1):35-48

Relevancia del adulterante activo cafeína en la acción estimulante de la pasta base de cocaína

Trabajo original

José Pedro Prieto María Noel Meikle Ximena López Hill Jessika Urbanavicius Giselle Prunell Juan Andrés Abín· Carriquiry María Cecilia Scorza

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1. To perform a chemical analysis of CP samples
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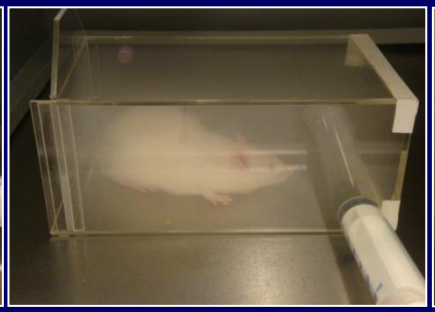
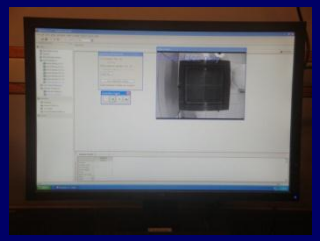
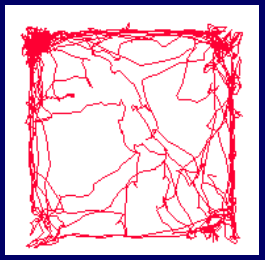
• ACUTE STIMULANT EFFECT BY VOLATILIZATION





Open field paradigm
+ Ethovision XP

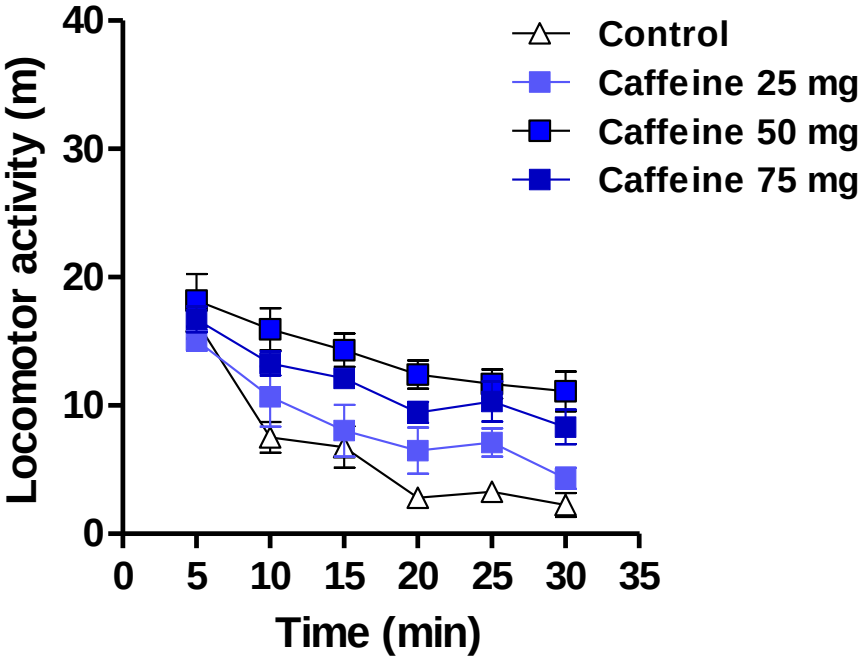


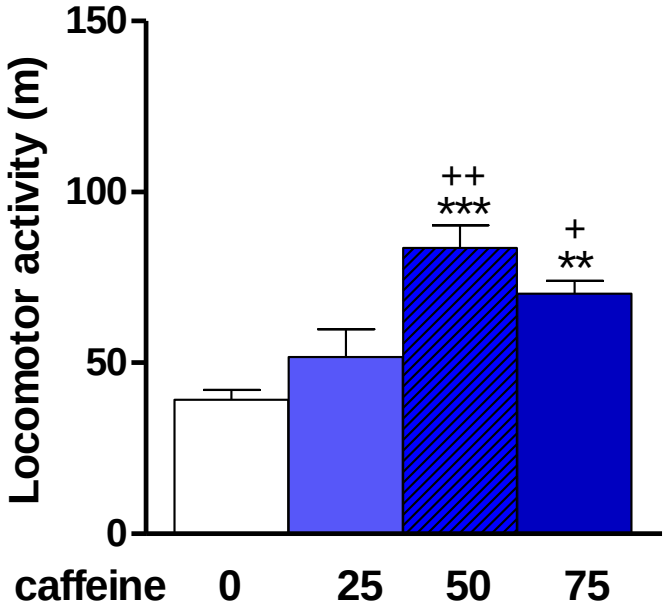
tracking

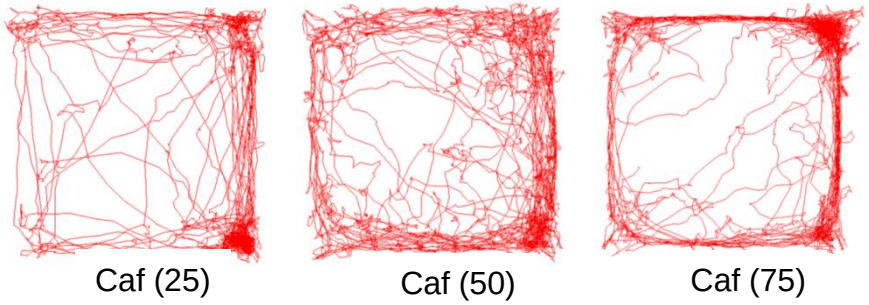
Pattern of movement
and distance moved (m)

RESULTS: *Caffeine volatilized (acute)*

Stimulant effect induced by volatilized caffeine

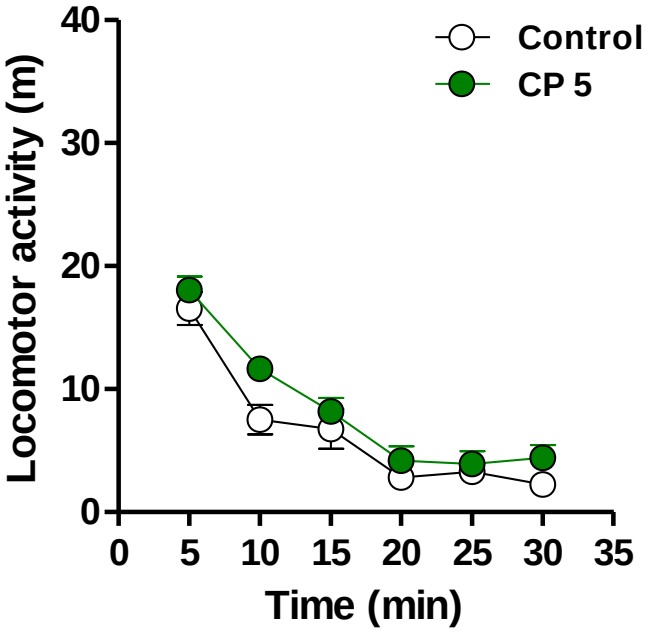


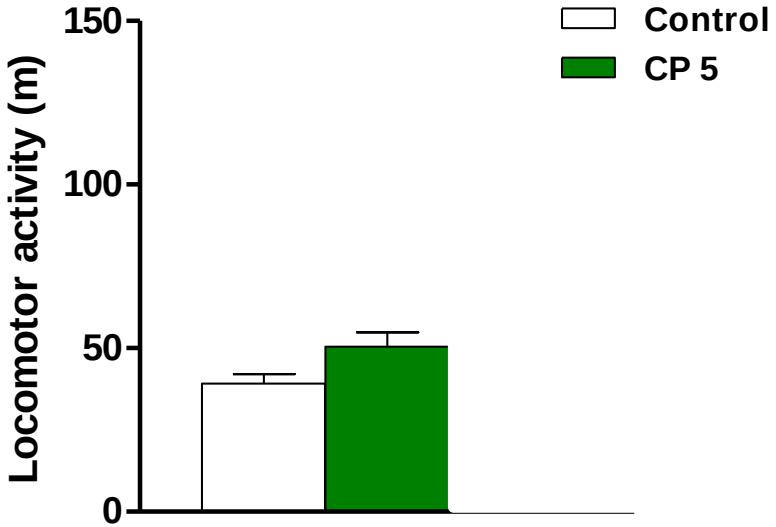


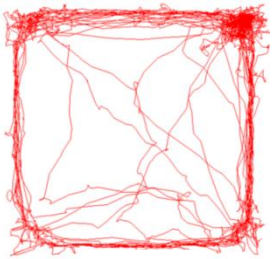


Galvalisi, Prieto et al. in progress

RESULTS III: *volatilized CP + caffeine (acute)*





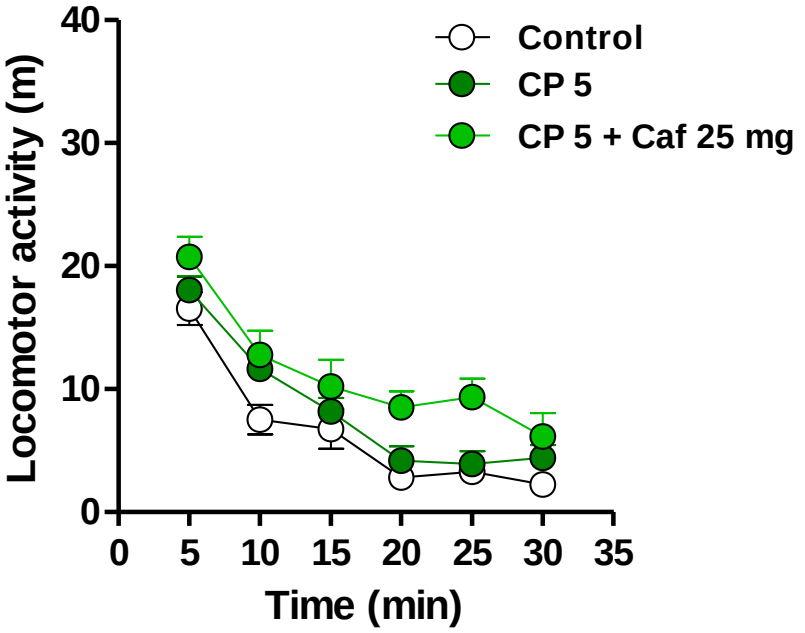


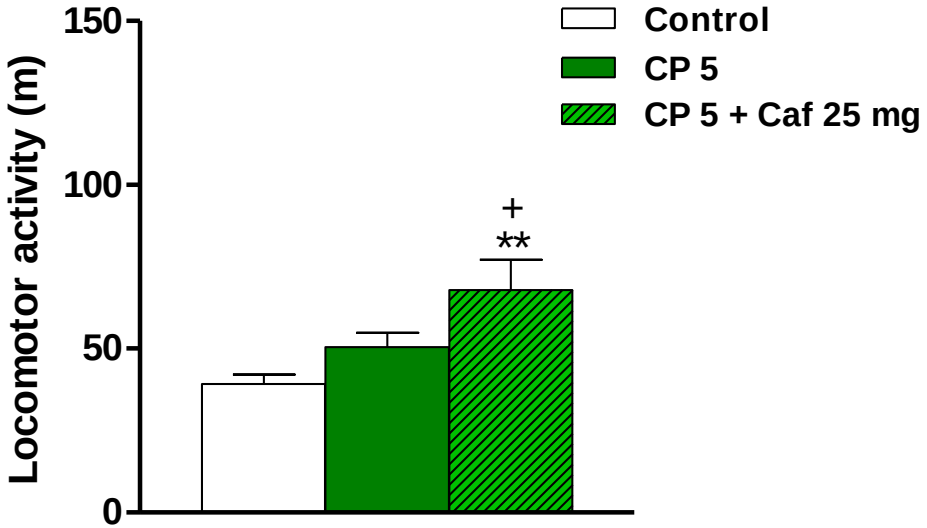
CP 5

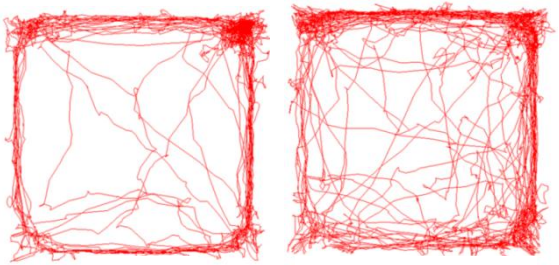
Galvalisi, Prieto et al. in progress

RESULTS III: *volatilized CP + caffeine (acute)*

Caffeine potentiated the CP stimulant effect

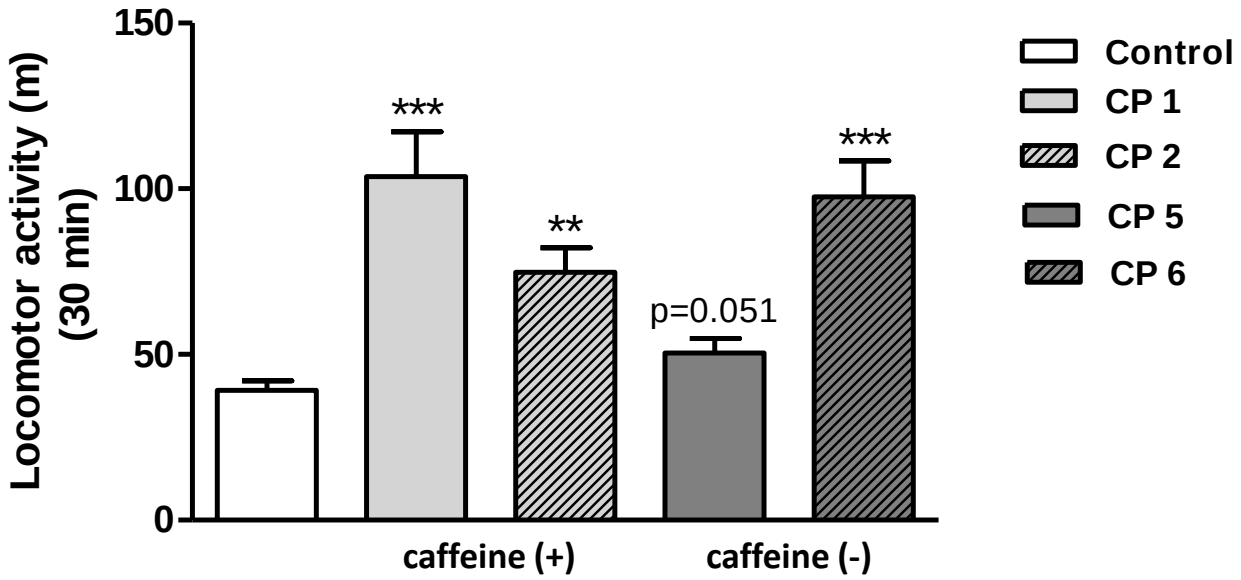


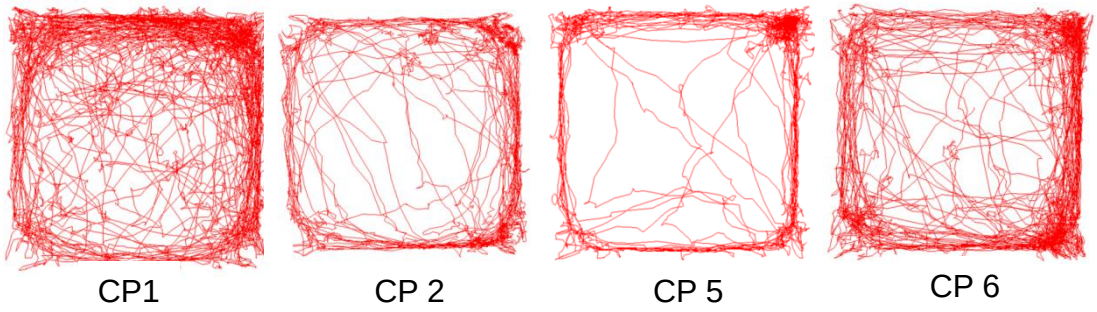




Galvalisi, Prieto et al. in progress

Stimulant effect induced by four different CP volatilized samples





Galvalisi, Prieto et al. in progress

CP

Chemical content determined

Volatilization of Cocaine + caffeine

Pyrolysis products

Depending of the volatilization temperature some products appear

temperature to be volatilized?

AEME= metilecgonidina (metil éster anhidroecgonina)

only appears when coceaine is smoked

Coca-Paste (volatilization)

COCAINE

CAFFEINE

OTHER COMPOUNDS

TEMPERATURE

1) Volatilized caffeine elicited a dose-dependent stimulant effect;
2) Caf was able to potentiate the CP 5-induced stimulant effect suggesting that the adulteration of CP samples with Caf may contribute to explain the high stimulation observed in CP users;

3) impurities cannot be excluded under this route of administration;
4) factors other than cocaine or caffeine should be taken into account since each CP samples induced a different behavioral response even under the same quantity of cocaine. Temperature of volatilization could be one important factor to explain these differences.

Initial questions …

- **What is Coca-Paste? √**
- **Is it a new drug of abuse in Latin America? √**
- **Is there any information about CP neurobiological actions? √**
- **Although it is a smokable form of cocaine, is it different to sniffed cocaine? √**
- **Can CP effects be explained only by the route of administration? √**

Participants and acknowledgments

MSc. Ma. Noel Meikle
Lic. Ximena López-Hill
MSc. Jessika Urbanavicius
Lic. José Pedro Prieto
Martín Galvalisi
Dra. Giselle Prunell
Dr. Andrés Abin-Carriquiry
Marcela Martínez
Dra. Cecilia Scorza

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Acknowledgments…

COLLABORATIONS

- **FACULTAD DE MEDICINA**: Pablo Torterolo, Patricia Lagos, Natalia, Horacio et al.
- **CENTRO DE MEDICINA NUCLEAR**: Rodolfo Ferrando, Andrés Damián, Verónica Depons.
- **CUDIM**: Patricia Oliver, Laura Reyes, Eduardo Savio, Henry Engler.
- **POLO TECNOLÓGICO**: Eleuterio Umpiérrez.
- **INSTITUTO TÉCNICO FORENSE**: QF. Elena Lerena**.**
- **JUNTA NACIONAL DE DROGAS**: Milton Romani, Laurita Regueira, Héctor Suárez.
- **Centro de Referencia Nacional de la Red Drogas "Portal Amarillo"**, Juan Triaca.
- **CLÍNICA PSIQUIÁTRICA, HOSPITAL VILARDEBÓ**: Sandra Romano.
- **UNIVERSIDAD DE BUENOS AIRES**: Ramón Bernabeu.
- **UNIVERSIDAD CATÓLICA DE CHILE**: José Fuentealba.
- **LARNEDA**
- **HOSPITAL PEREIRA ROSSEL**: Dr. Mario Moraes.
- **Dra. Andrea Gago.**

Thanks!

BEHAVIORAL SENSITIZATION

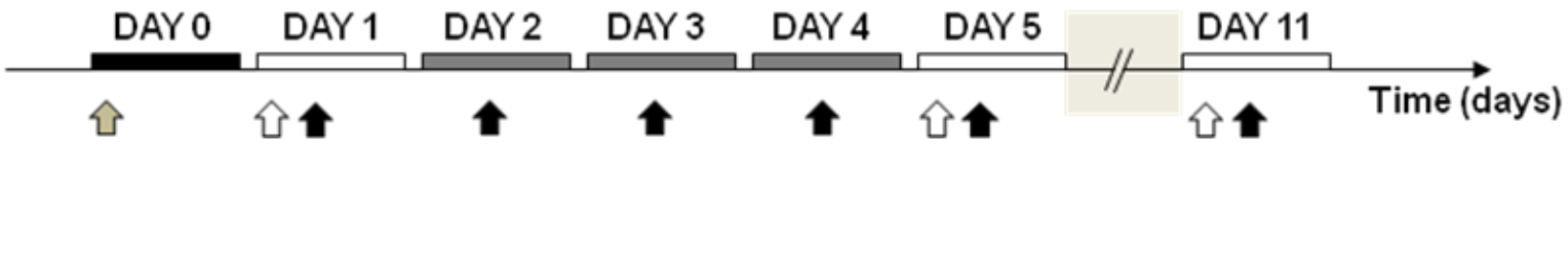
Repeated exposure to psychomotor stimulant drugs produces *behavioral sensitization*, a progressive and enduring augmentation of locomotor responses to the drug after a withdrawal period and the re-exposure to the drug.

This phenomenon has been proposed to underlie rewarding drug effect, craving and relapse induced by pychostimulants.

Pierce C and Kalivas PA. *Brain Research Reviews* ,1997

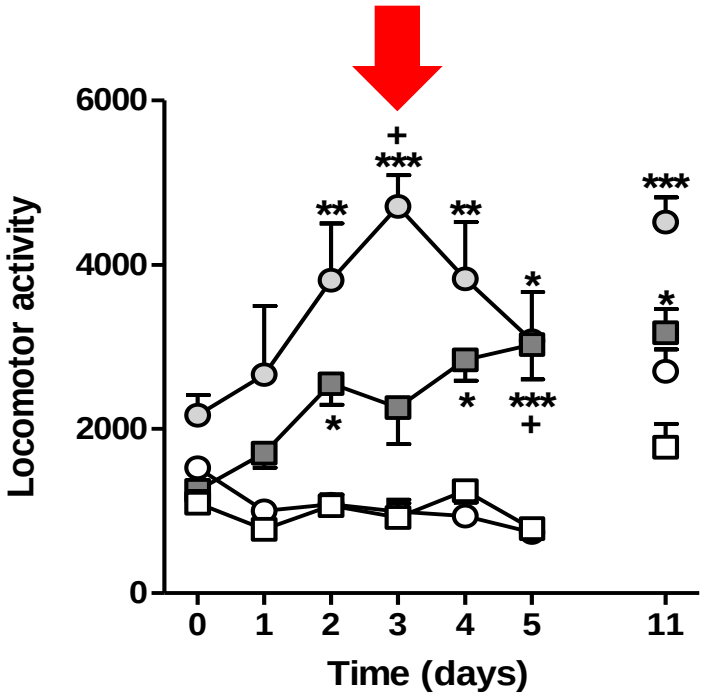
Behavioral sensitization

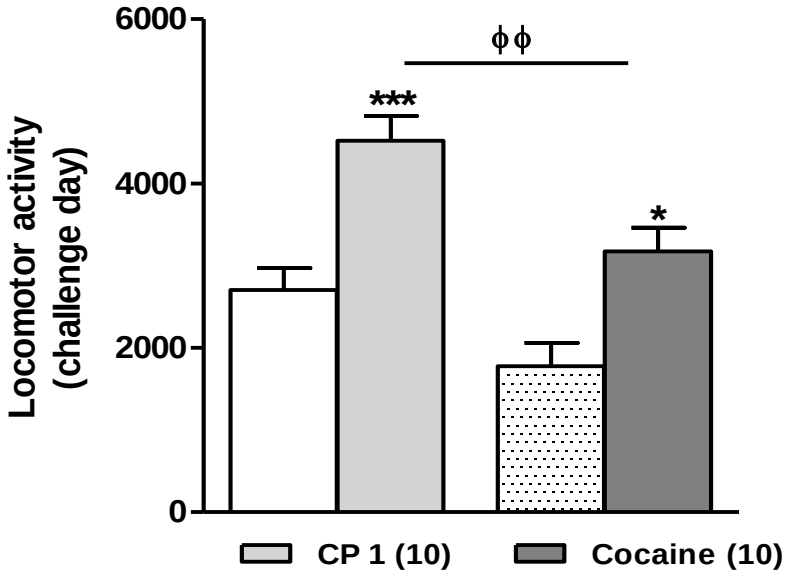
Experimental Protocol I



RESULTS: *locomotor sensitization induced by CP1 and Cocaine (repeated)*

A HIGH EXPRESSION OF SENSITIZATION WAS ELICITED BY COCA-PASTE COMPARED TO COCAINE





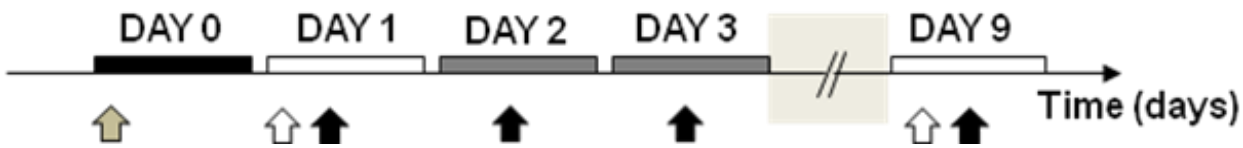
Cocaine is partially responsible since caffeine seems to collaborate in it

CP 1 (5 x eq. 10 mg/kg;
Cocaine (5 x 10 mg/kg

Sample	Cocaine	Caffeine
CP 1	68.9	15.0

Prieto et al. in preparation 2012

Experimental Protocol II



OF habituation session (60 min)

OF habituation session (20 min)

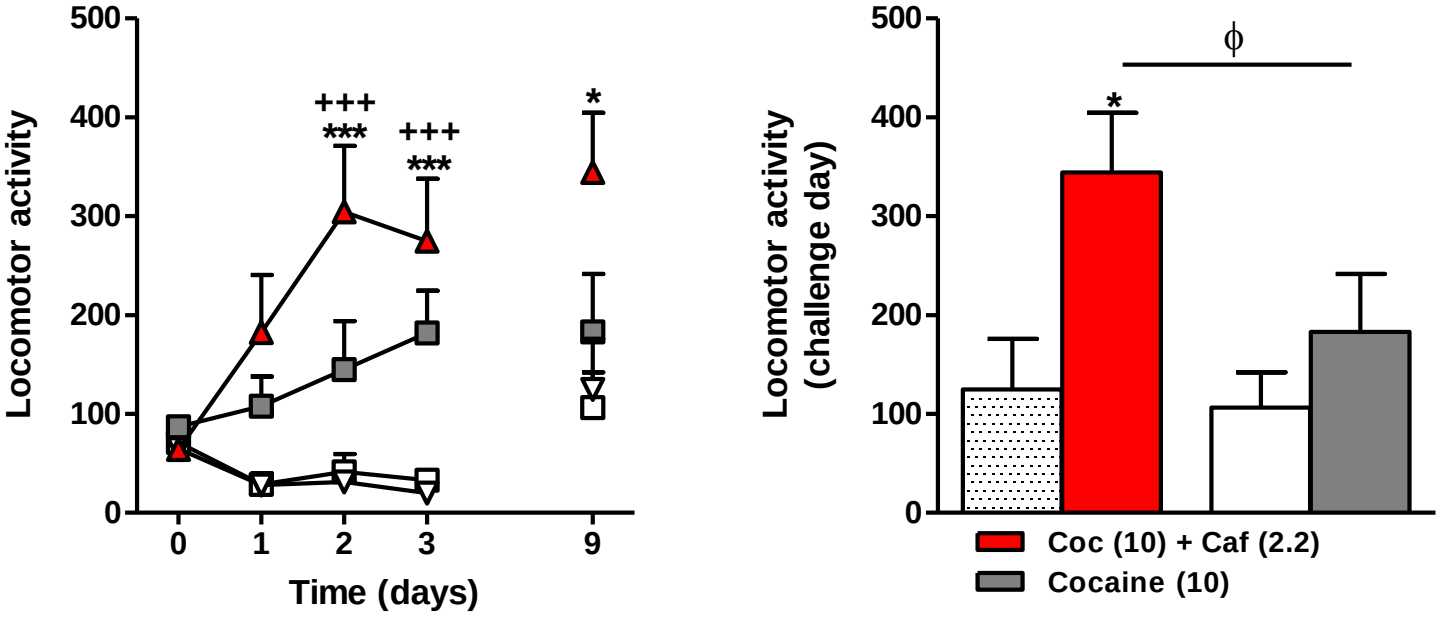
IP Injection of drugs or vehicle

Withdrawal period of 5 days

Sample PBC	Equivalent dose to cocaine base (mg/kg)	Dose of Caffeine (mg/kg)
CP 1	5	1.1
	10	**2.2**
	20	4.5

RESULTS: *locomotor sensitization induced by surrogate of CP 1 (repeated)*

CAFFEINE ACCELERATES THE EXPRESSION OF THE COCAINE-INDUCED SENSITIZATION



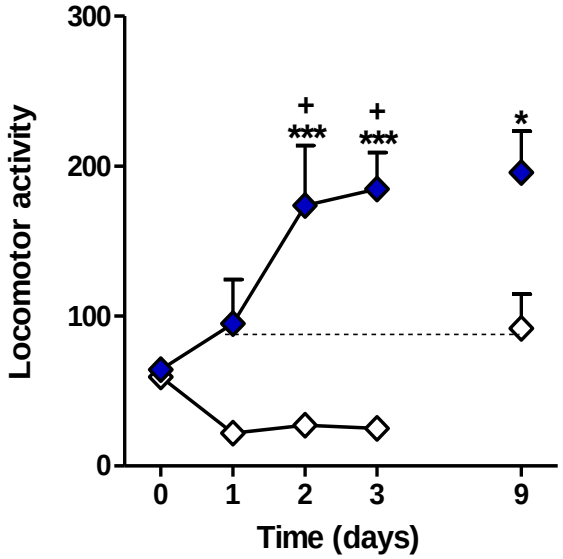
After 3 days of cocaine + caffeine co-administration, animals become sensitized. Caffeine seems to facilitate this phenomenon

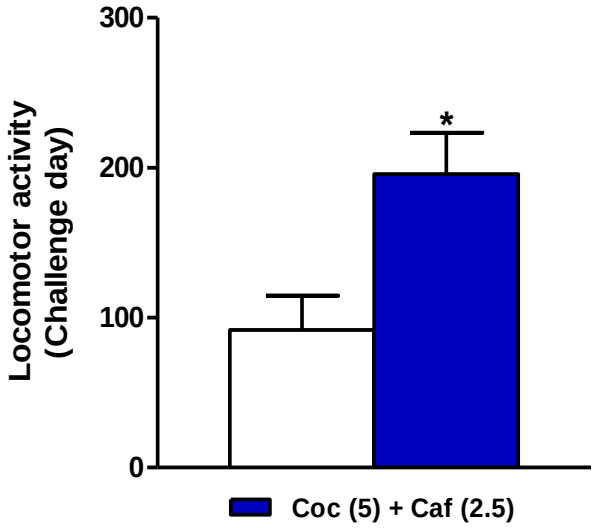
Cocaine + Caffeine [3 x Coc (10 mg/kg) + Caf (2.2 mg/kg)]

Prieto et al. in preparation 2012

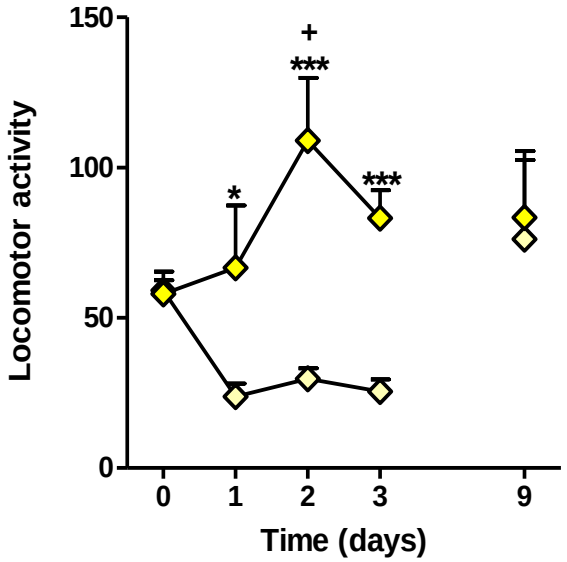
RESULTS: *locomotor sensitization induced by surrogate of CP 7 (repeated)*

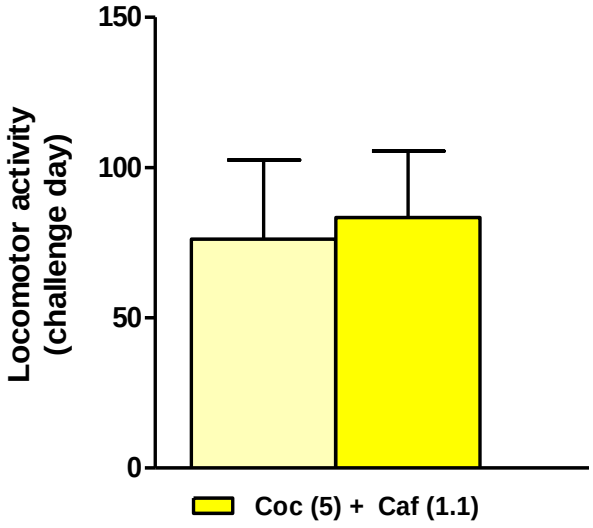
Cocaine + Caffeine
[(3 x Coc (5 mg/kg) +
Caf (2.5 mg/kg)]





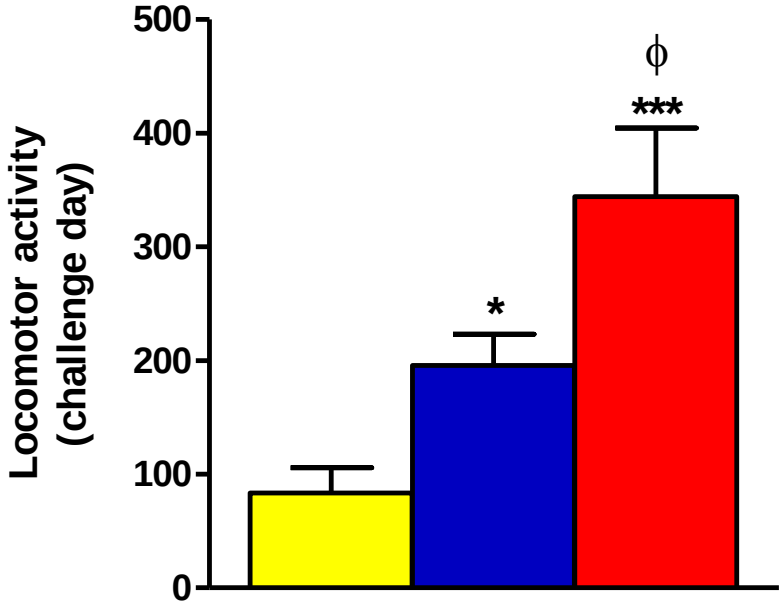
Cocaine + Caffeine
[(3 x Coc (5 mg/kg) +
Caf (1.1 mg/kg)]





Prieto et al. in preparation 2012

CAFFEINE POTENTIATES THE SENSITIZATION INDUCED BY COCAINE



Comparison between animals repeatedly treated with Cocaine + Caffeine [3 x Coc (5 mg/kg) + Caf (1.1 mg/kg)]; Cocaine + Caffeine [3 x Coc (5 mg/kg) + Caf (2.5 mg/kg)] and Cocaine + Caffeine [3 x Coc (10 mg/kg) + Caf (2.2 mg/kg)] **Although a dose-dependence could be noticed, caffeine contributed to the expression of sensitization induced by cocaine**. *= vs. Coc (5) + Caf (1.1); ϕ= Coc (10) + Caf (2.2) vs. Coc (5) + Caf (2.5). *** = P < 0.001; *, ϕ = P < 0.05.

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Research paper

Composition, purity and perceived quality of street cocaine in France

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Table 1
Main adulterants detected in the 343 samples containing cocaine. One or more adulterants can be present in each powder.

Name	Nature	Frequency	% Samples
Phenacetin	Antipyretic, analgesic	184	54
Caffeine	Psychostimulant	62	17
Paracetamol	Antipyretic, analgesic	48	14
Diltiazem	Calcium blocker	37	11
Lidocaine	Local anesthetic	36	11
Levamisol	Antiparasitic agent	21	6
Hydroxyzine	H1 antihistaminergic	12	4
Acetylsalicylic acid	Antipyretic, analgesic	6	2
Propoxyphen	Analgesic	6	2
At least one adulterant		251	73

Caffeina:

• **Caffeine** is the most consumed psychoactive drug in the world.

• **Caffeine**, amphetamine and lidocaine are very common active adulterants found in illicit drugs, including cocaine.

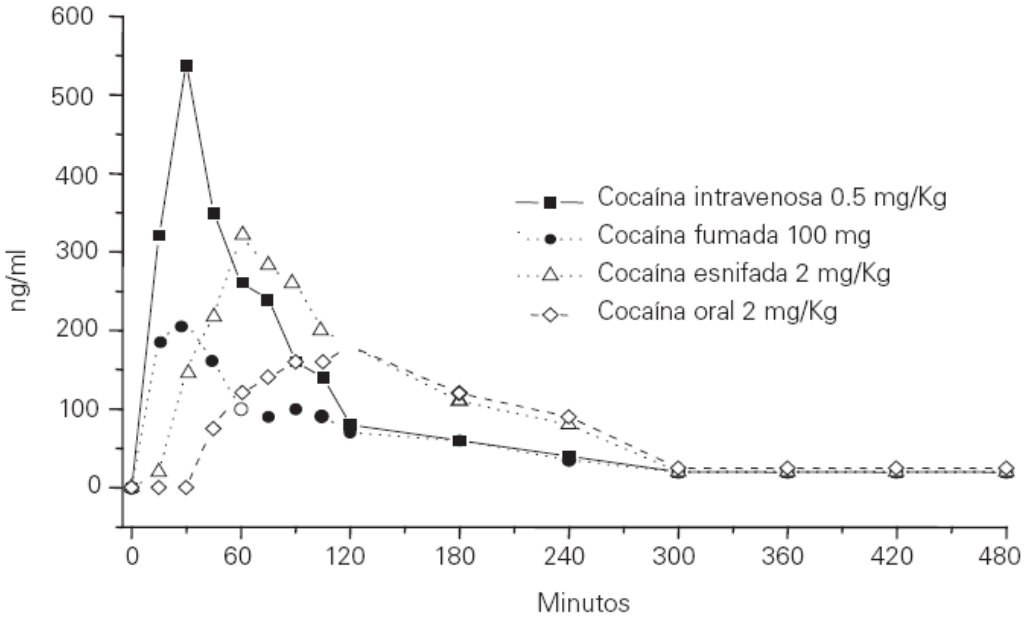
• In human, low non-toxic doses of **caffeine** produce positive effects on arousal, vigilance and attention whereas higher doses cause anxiety, nervousness, impaired thinking, sleep disturbance, heart palpitations and stomach irritation; toxic doses provoke seizures.

• acute systemic administration of **caffeine** can increase the cocaine induced locomotor stimulant activity indicating an additive action of both drugs.

• **Mechanism of action: non selective antagonist of adenosine A2 and A1 receptors**. Modulates DA neurotransmission, facilitating the DA release. Effect related with drugs of abuse dependence.

• **"black magic"** - **crude freebase caffeine**. Smoking caffeine, a rapid rash like freebase cocaine. http://boingboing.net/2009/01/19/how-to-make-smokable.html

Figura 1. Niveles plasmáticos de cocaína



(Modificado de Jones 1998)

Lizasoain y col. Adicciones 1999.

Table 2
Effects on distance moved and velocity of movement induced by systemic administration of CP samples, cocaine, caffeine or the combination between cocaine and caffeine treatments at different doses.

Treatment	Mean ± SEM of distance moved (m)	Mean ± SEM of velocity (m/s)
Control	55.6 ± 4.3	0.01 ± 0.001
Cocaine (5)	143.4 ± 11.1***	0.04 ± 0.003***
CP 1 (5)	167.6 ± 9.1***	0.05 ± 0.002***
CP 5 (5)	133.9 ± 11.8***	0.03 ± 0.004***
CP 7 (5)	198.9 ± 16.4$^{***++//}$	0.06 ± 0.004$^{***++//}$
Coc (5) + Caf (2.5)	191.3 ± 19.1$^{***++###}$	0.06 ± 0.005$^{***++###}$
Caffeine (2.5)	86.2 ± 10.9^{++}	0.02 ± 0.003^{++}
Cocaine (20)	323.0 ± 25.8***	0.09 ± 0.007***
CP 1 (20)	425.2 ± 22.2$^{***++///}$	0.12 ± 0.006$^{***++///}$
CP 5 (20)	261.6 ± 38.2***	0.07 ± 0.010***
Coc (20) + Caf (4.5)	414.9 ± 38.4$^{***+###}$	0.12 ± 0.010$^{***+###}$
Caffeine (4.5)	119.9 ± 9.1^{+++}	0.03 ± 0.002^{+++}

Table shows the effect of the systemic administration of CP 1, 5, 7 samples at equivalent doses of cocaine base (5 and 20 mg/kg); Cocaine at 5 and 20 mg/kg; Caffeine at 2.5 and 4.5 mg/kg; Cocaine at 5 mg/kg combined with Caffeine at 2.5 mg/kg, Coc (5) + Caf (2.5) and Cocaine at 20 mg/kg combined with Caffeine at 4.5 mg/kg, Coc (20) + Caf (4.5), on the distance moved and movement velocity during 60 min. All data are expressed as mean ± SEM. One-way ANOVA followed by Newman–Keuls test. * = denotes statistical differences vs. control group; $^{+}$ = denotes statistical differences vs. Cocaine (5 or 20 mg/kg). $^{/}$ = denotes statistical differences between CP samples. $^{\#}$ = denotes statistical differences vs. Caffeine (2.5 or 4.5 mg/kg). $^{***,+++,///,\#\#\#}$ = $P < 0.0001$; $^{++//}$ = $P < 0.01$; $^{+}$ = $P < 0.05$. N = 5–8.

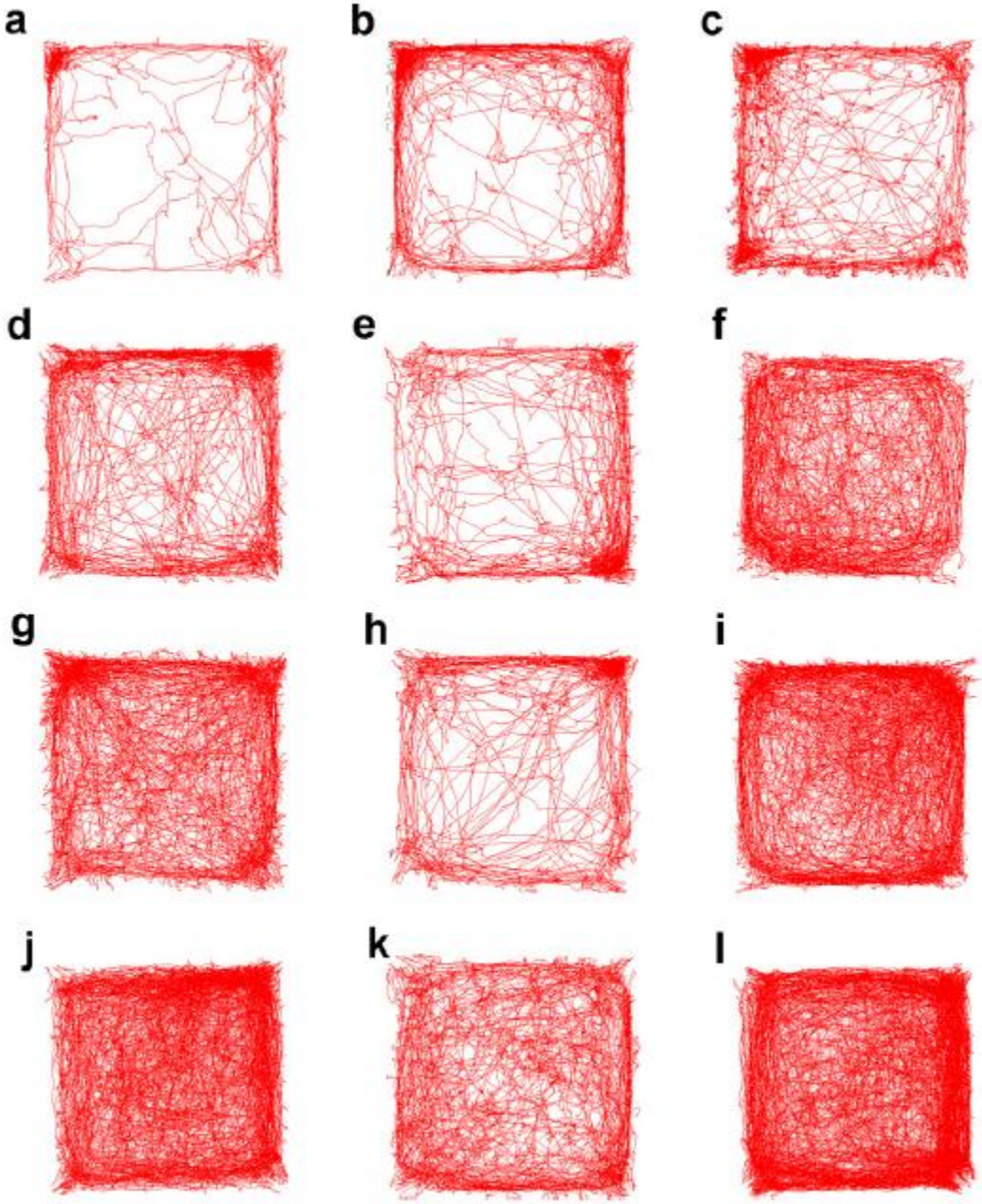


Fig. 5. Pattern of movement induced by cocaine, CP 1, CP 5, CP 7 or combined treatment of cocaine plus caffeine, at different doses. Red traces represent the animal locomotion under each treatment (a–l) recorded during 60 min. a: control group; b: caffeine (2.5); c: cocaine (5); d: CP 1 (5); e: CP 5 (5); f: CP 7 (5); g: Coc (5) + Caf (2.5); h: caffeine (4.5); i: cocaine (20); j: CP 1 (20); k: CP 5 (20); l: Coc (20) + Caf (4.5). Numerical data corresponding to each trace are showed in Table 2. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

The Journal of Neuroscience, August 1, 2002, 22(15):6321–6324

Brief Communication

Caffeine Induces Dopamine and Glutamate Release in the Shell of the Nucleus Accumbens

Marcello Solinas,[1] Sergi Ferré,[1] Zhi-Bing You,[2] Marzena Karcz-Kubicha,[1] Patrizia Popoli,[3] and Steven R. Goldberg[1]

Sections of [1]Preclinical Pharmacology and [2]Behavioral Neuroscience, Behavioral Neuroscience Branch, National Institute on Drug Abuse, National Institutes of Health Intramural Research Program, Baltimore, Maryland 21224, and [3]Department of Pharmacology, Istituto Superiore di Sanita, 00161 Rome, Italy

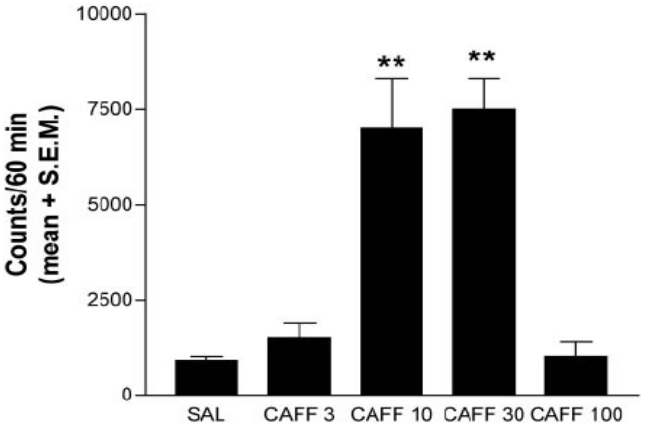


Figure 1. Total horizontal motor activity after intraperitoneal administration of caffeine in habituated rats. The results represent means ± SEM of the accumulated motor activity counts during the first 60 min period of observation ($n = 6$ per group). Significant motor activation was obtained with caffeine in a dose of 10 mg/kg (*CAFF 10*) and caffeine in a dose of 30 mg/kg (*CAFF 30*). $^{**}p < 0.01$ compared with the group treated with saline (*SAL*).*CAFF 3* and *CAFF 100* indicate 3 and 100 mg/kg caffeine, respectively.

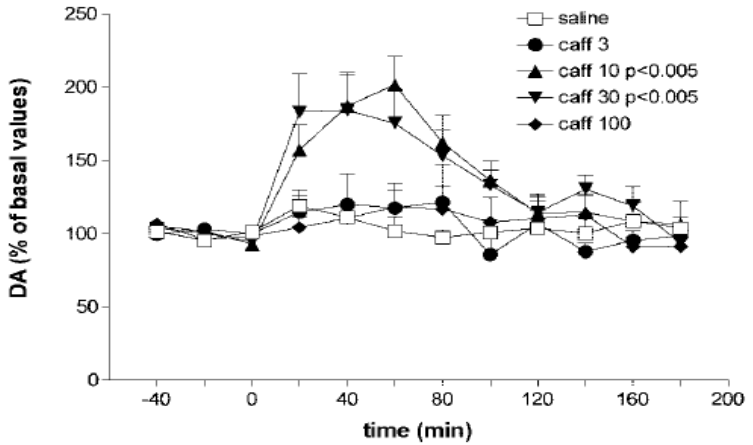


Figure 2. Extracellular concentrations of dopamine (*DA*) and glutamate (*Glu*) in the shell of the NAc after intraperitoneal administration of saline or caffeine [3 (*caff 3*), 10 (*caff 10*), 30 (*caff 30*), or 100 (*caff 100*) mg/kg]. The results represent means ± SEM of the percentage of basal values of the extracellular concentrations of dopamine and glutamate ($n = 6–8$ per group). Basal values were the means of three values before drug administration. Caffeine at doses of 10 and 30 mg/kg but not at doses of 3 and 100 mg/kg significantly increased the extracellular levels of dopamine and glutamate (Student's paired t test; only significant results of pretreatment vs post-treatment are shown).

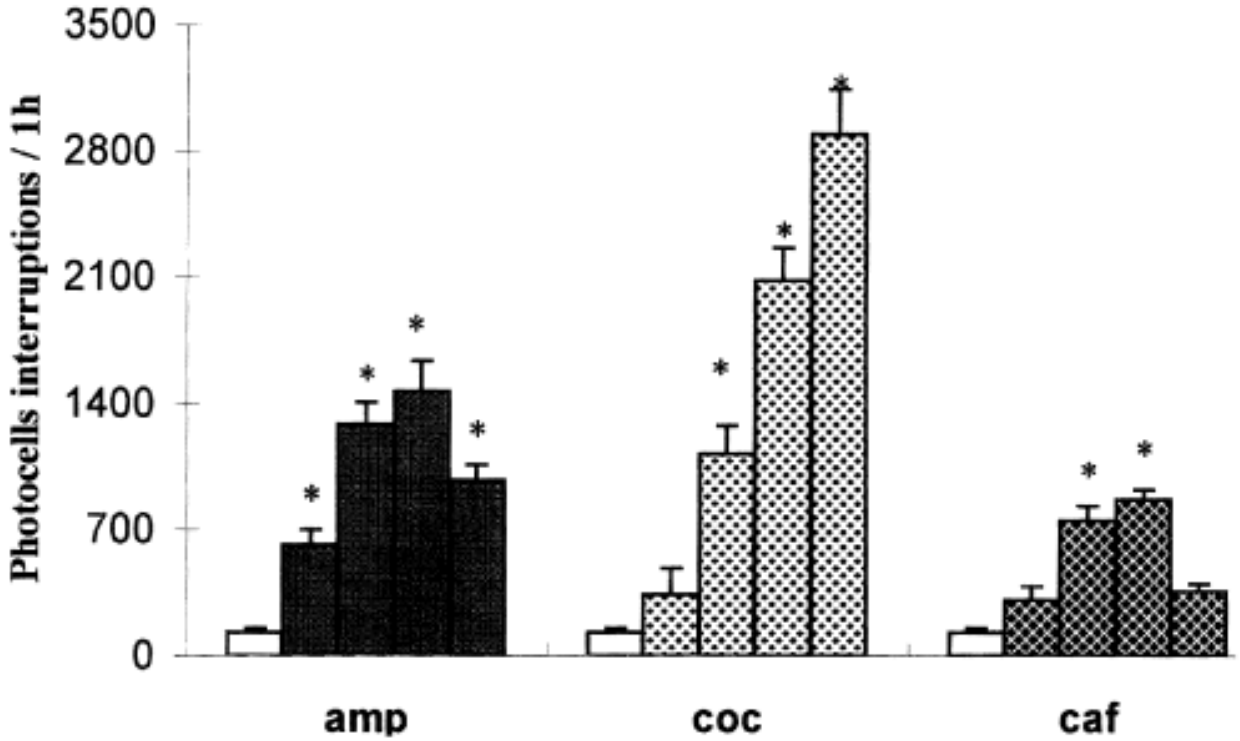
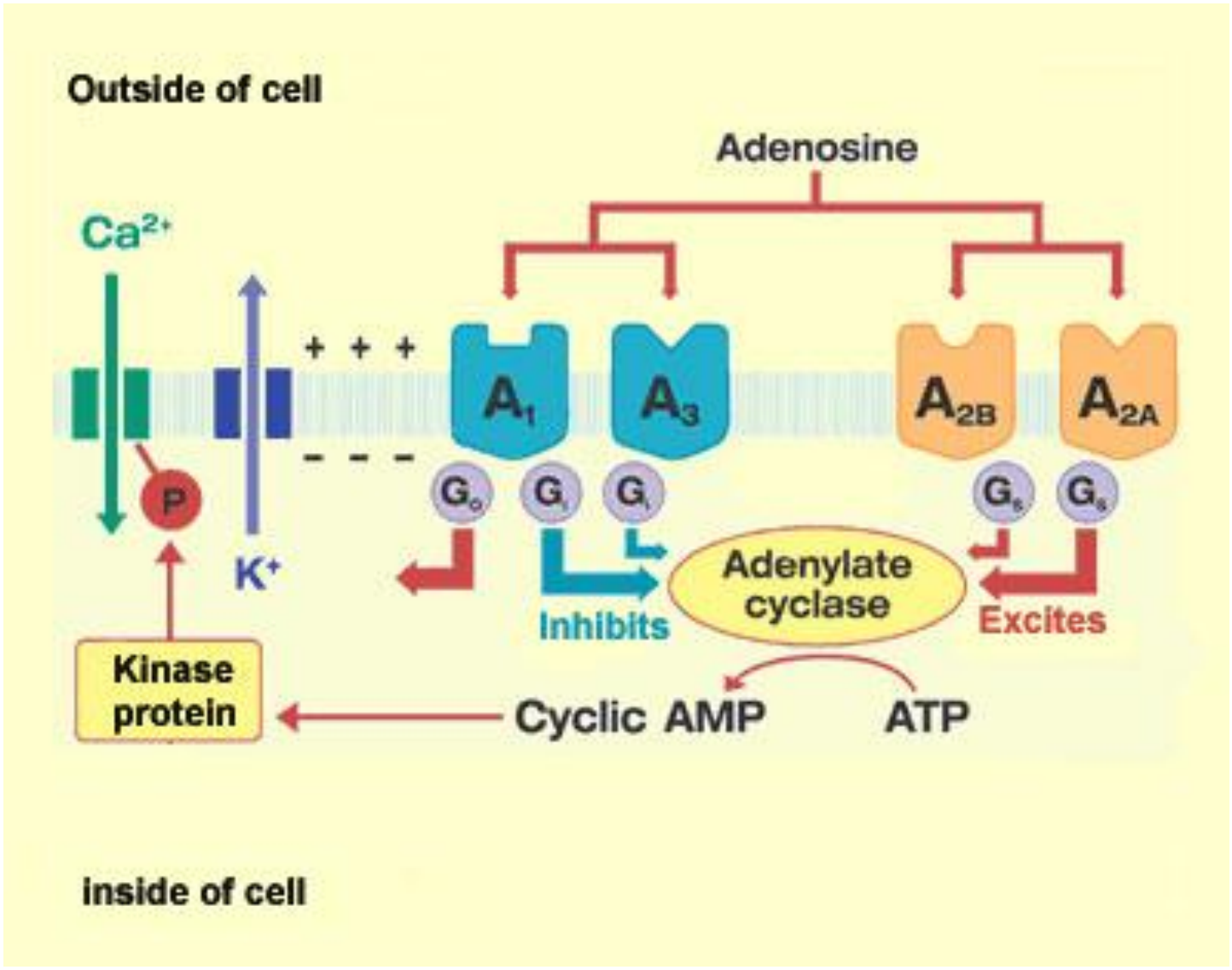


Fig. 1. Effects of d-amphetamine (amp: saline, 0.5, 1.5, 3 and 6 mg/kg), cocaine (coc: saline, 5, 10, 20 and 50 mg/kg), and caffeine (caf: saline, 5, 10, 20 and 40 mg/kg) on photobeam interruptions, in a continuous 1 h recording session. $^{*}p < 0.01$ with respect to saline group.

Antoniou et al. Neuroscience and Biobehavioral Reviews,1998.


Outside of cell
Adenosine
Ca2+
+ + +
A1
A3
A2B
A2A
P
K+
Adenylate cyclase
Inhibits
Excites
Kinase protein
Cyclic AMP
ATP
inside of cell

Sistema DAérgico y ganglios basales

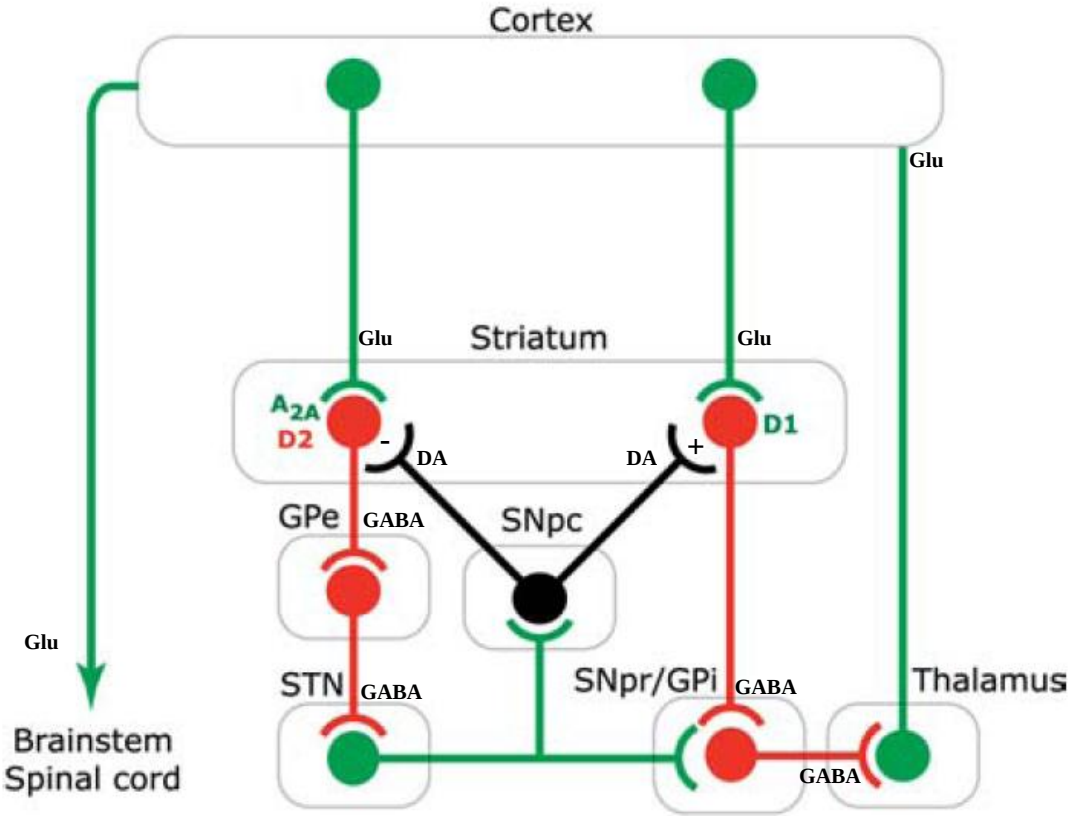


Figure 1. Diagram illustrating the functional organization of the basal ganglia. The striatum receives an excitatory glutamatergic input (green) from cerebral cortex and a modulatory dopaminergic input (black) from the substantia nigra pars compacta (SNpc). GABAergic striatal medium spiny neurons innervate either directly or indirectly [via globus pallidus pars externa (Gpe) and subthalamic nucleus (STN)] the substantia nigra pars reticulata (SNpr)/ globus pallidus pars interna (Gpi). Dopamine activates, via D_1 receptors, the direct striato-nigral/Gpi pathway and inhibits, via D_2 receptors, the indirect striato-Gpe pathway. These opposite regulations disinhibit thalamo-cortical glutamatergic neurons and promote motor activity. Adenosine, via A_{2A} receptors, antagonizes the inhibitory effect of dopamine D_2 receptors on the indirect pathway, thereby depressing motor activity. Caffeine produces its psychomotor stimulant effect by blocking adenosine A_{2A} receptors. In addition, caffeine may protect SNpr/Gpi dopaminergic neurons from glutamate-induced neurotoxicity via disinhibition of GABAergic Gpe neurons and inhibition of STN neurons (cf. text). Excitatory (glutamatergic) and inhibitory (GABAergic) inputs are shown in green and red, respectively.

CHEMICAL ANALYSIS

A first step of identification of cis- and trans-cinnamoylcocaine, metilecgonine, cocaine and adulterants in CP samples was performed using a **Gas Chromatograph with a Mass selective detector.**

A high performance liquid chromatography with **Diode Array Detector (HPLC-DAD)** was performed to quantify the percentage of cocaine and caffeine in each CP samples.

Few evidences about the chemical composition of CP samples

ElSohly et al. “Coca-Paste: chemical analysis and smoking experiments” (*J. of Forensic Sciences*, 1991). CP from Perú and Colombia

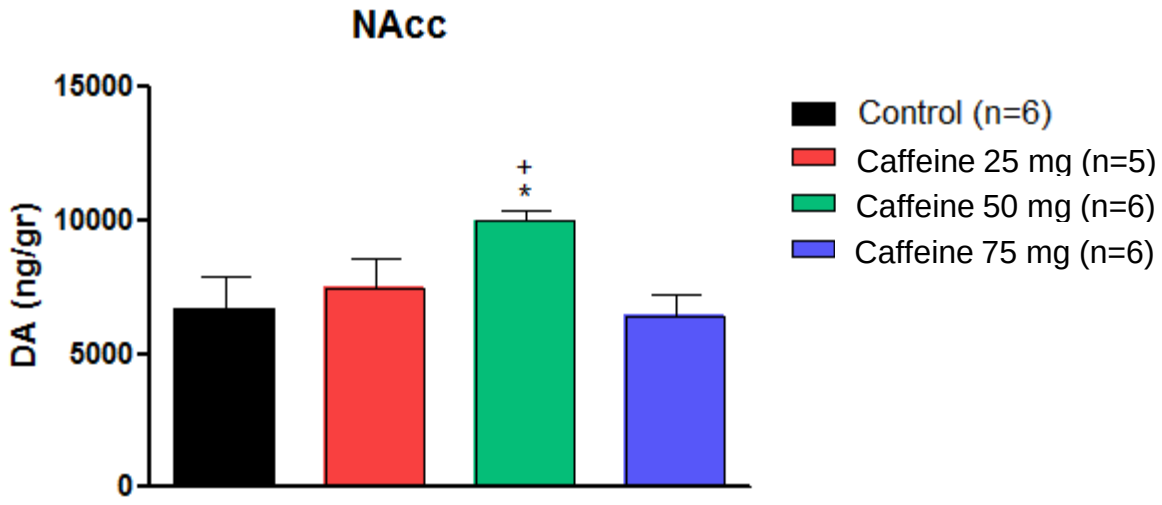
- Cocaine (80 -90 %)
- manganese/plumb, cis-cinamoylcocaine; trans-cinamoylcocaine
- authors do not report if CP contained adulerants

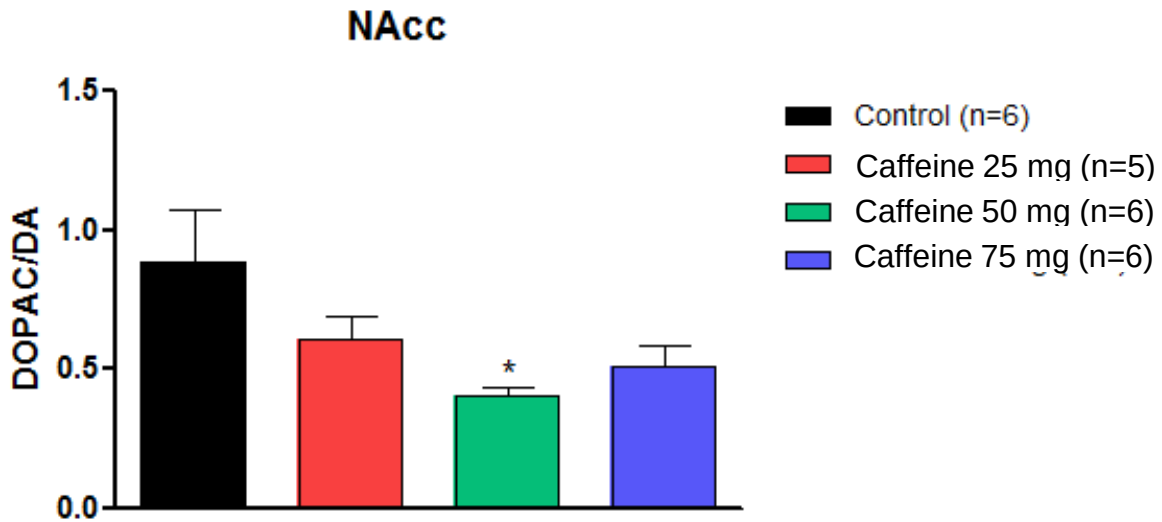
Eleuterio Umpiérrez. Laboratorio de Análisis Orgánico-Facultad de Química-Polo Tecnológico de Pando- UdelaR (2005-2006)

- Cocaína (30-70 %)
- benzoato de metilo, Benzilecgonine, ecgonine, Nor-cocaine;
- cis-cinamoylcocaine, trans-cinamoylcocaína, truxilinas, tropocaína.
- authorsdo not report if CP contained adulerants

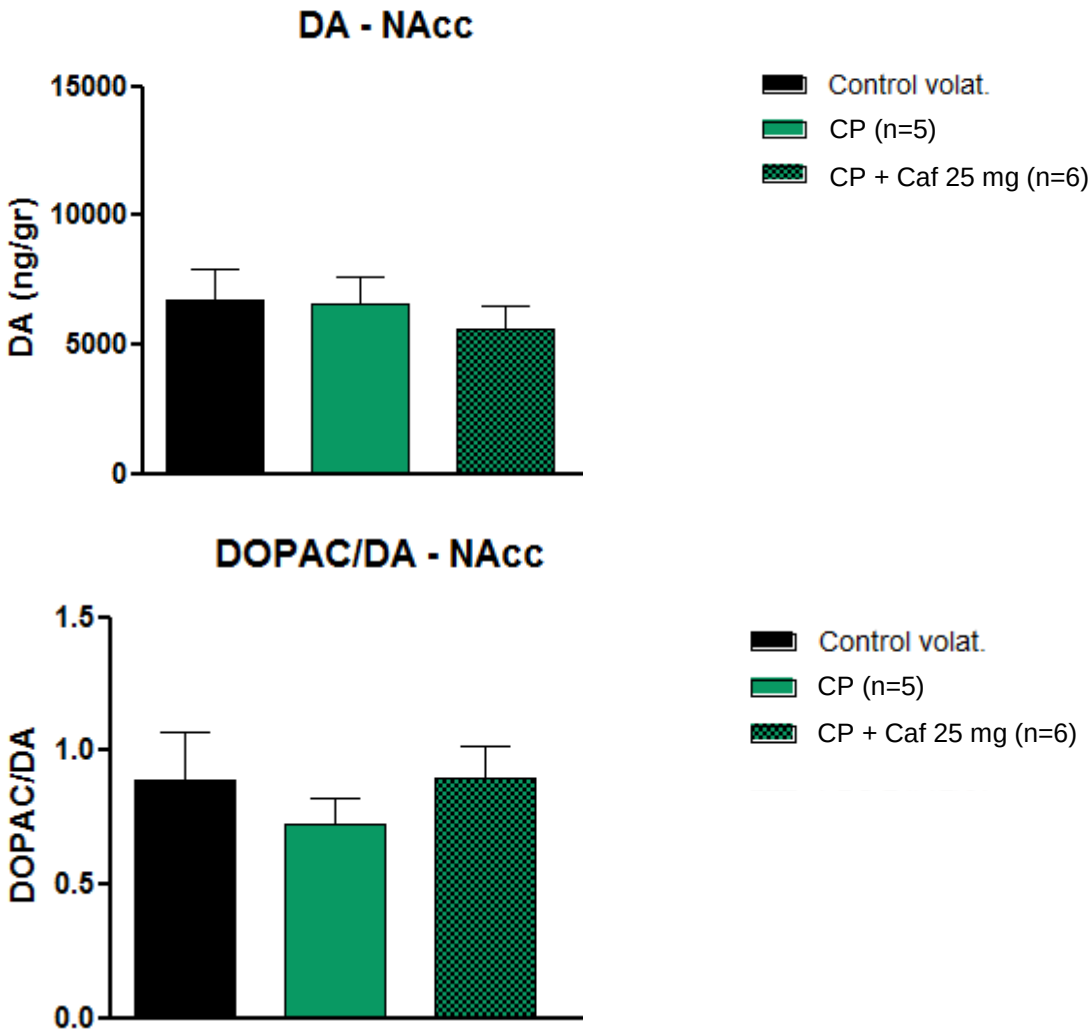
Chemical composition can vary according to the samples origin

RESULTS: *Neurochemical effect induced by Caffeine on DA levels in NAcc*

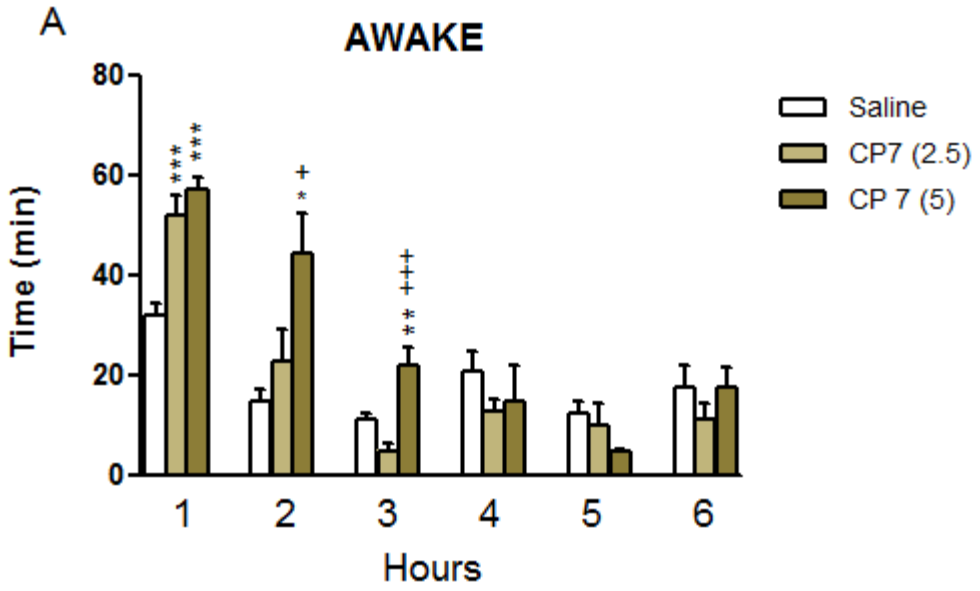


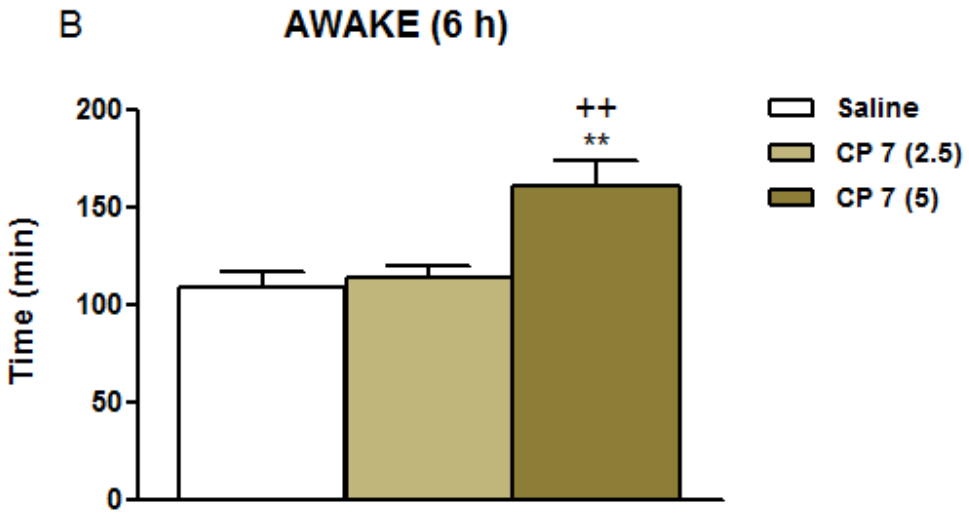


RESULTS: *Neurochemical effect induced by a CP sample plus caffeine on DA levels in NAcc*

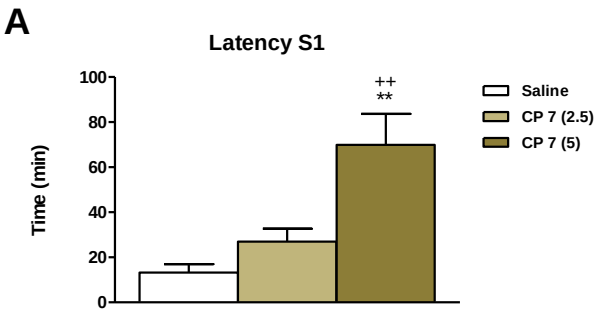


Galvalisi, Prieto et al. no published, 2012





Schwarzkopf, Igarzabal y cols. Datos no publicados, 2012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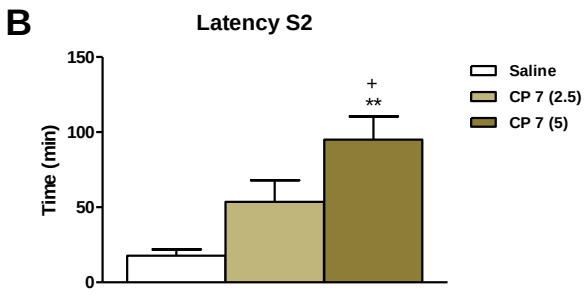
++
**
Saline
CP 7 (2.5)
CP 7 (5)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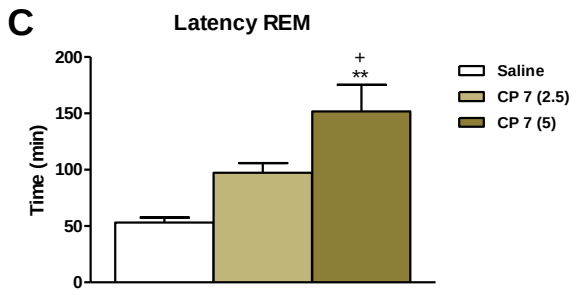
CP 7 (2.5)
CP 7 (5)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Saline
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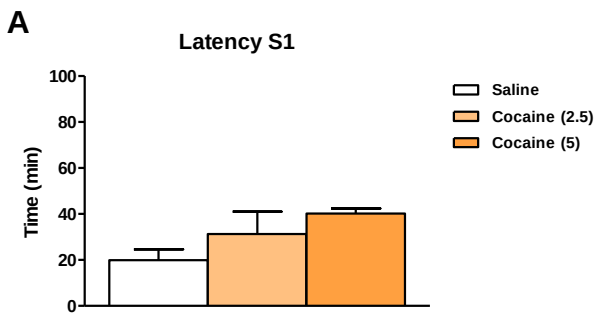
CP 7 (5)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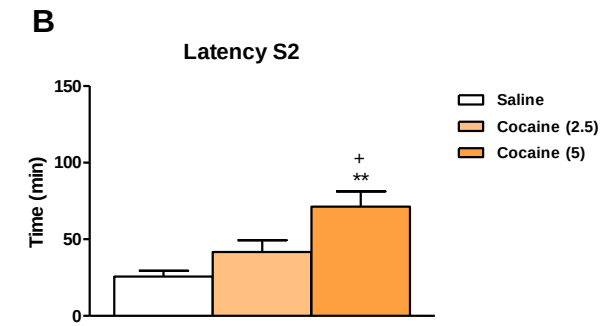
Saline
Cocaine (2.5)
Cocaine (5)


B
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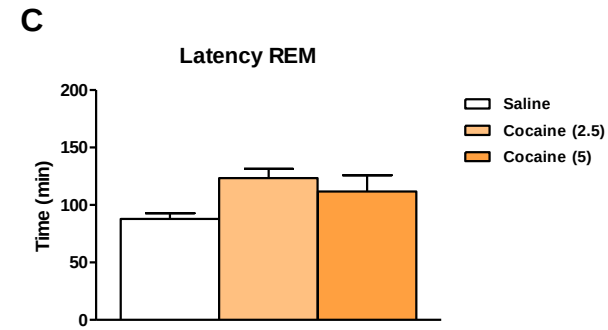
Saline
Cocaine (2.5)
Cocaine (5)


C
Latency REM
Time (min)
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Saline
Cocaine (2.5)
Cocaine (5)