# Efecto de la Ibogaína sobre la Vigilia y el Sueño

Informe de Pasantía

Licenciatura en Biología Humana

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«DESDE ENTONCES EN ELEUSIS , EN HONOR DE LA DIOSA SE CELEBRAN LOS MISTERIOS QUE NO SE PUEDEN CONTAR. ¡FELICES AQUELLOS HOMBRES QUE LOS HAYAN CONOCIDO!»

Himno Homérico a Demeter,
siglo VII a.C [1]

[1]Los misterios eleusinos se celebraron desde 1500 a.C hasta su cierre en el año 392 d.C. Durante los misterios se consumía una bebida especial a base de cebada llamada ¨kykeon¨, se ha propuesto que la cebada puede haber contenido al hongo *Claviceps purpurea*, del cual se derivo originalmente el LSD.

# Agradecimientos

En primer lugar, quiero agradecer a Ignacio Carrera, por introducirme al estudio de la ibogaína y proveerme amablemente la sustancia orgánica para la realización de este trabajo.

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**Resumen**

La ibogaína es un potente alcaloide psicodélico que ha sido el foco de una intensa investigación debido a sus intrigantes propiedades antiadictivas. Según informes anecdóticos, la ibogaína se clasificó originalmente como psicodélica oneirogénica; es decir, induce una actividad cognitiva similar a un sueño mientras se está despierto. Sin embargo, los efectos de la administración de ibogaína en la vigilia (W) y el sueño no se han evaluado a fondo. Por lo tanto el objetivo de nuestro estudio fue caracterizar los efectos agudos de la administración de ibogaína sobre W y el sueño. Para este propósito, se realizaron registros polisomnográficos en ratas implantadas crónicamente durante la fase de luz durante 6 hs. Los animales fueron tratados con ibogaína (20 y 40 mg / kg) o vehículo, inmediatamente antes del comienzo de las sesiones experimentales. En comparación con el control, los animales tratados con ibogaína mostraron un aumento en el tiempo pasado en W. Este efecto fue acompañado por una disminución en el sueño de ondas lentas (SWS) y el tiempo de sueño de movimientos oculares rápidos (REM). La latencia del sueño REM aumentó significativamente en los animales tratados con la dosis de ibogaína más alta. Mientras que los efectos en W y SWS se observaron durante las primeras 2 hs de registro, la disminución en el tiempo de sueño REM se observó durante todo el tiempo de registro. Concluimos que la ibogaína promueve un estado de vigilia que se acompaña de una supresión del sueño REM robusta y duradera. Dado que la ibogaína se metaboliza para producir noribogaína, se necesitan más experimentos para dilucidar si el metabolito y / o el fármaco original produjeron estos efectos.

***Palabras Clave***— ibogaína, vigilia, sueño REM, psicodélicos

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# 1. Introducción

## 1.1. Ciclo Sueño-Vigilia

El ciclo sueño-vigilia es el ritmo biológico más evidente en las aves y los mamíferos. Dicho ciclo está compuesto por dos estados comportamentales: la vigilia (W, del inglés wakefulness) y el sueño, que poseen diferencias tanto fisiológicas como comportamentales (Kryger et al., 2011). El ciclo sueño-vigilia sigue un ritmo circadiano. El marcapaso o reloj interno de este ritmo es el núcleo supraquiasmático, el cual está modulado por la luz a través de proyecciones provenientes de la retina (Mistlberger, 2005). El sueño se puede definir como un estado reversible donde la respuesta y la interacción con el medio se encuentran disminuidas. Durante este se distinguen dos grandes estados: el sueño no-REM (NREM) o sueño lento, y el sueño REM (del inglés: "rapid eye movements") (Kryger et al., 2011). Desde el punto de vista electroencefalográfico (EEG) la vigilia se caracteriza por una activación del neocortex, evidenciado por un aumento de la frecuencia y una disminución de la amplitud del trazado. La presencia de tono muscular es reflejada en la alta amplitud en el electromiograma (EMG). El sueño NREM presenta en forma característica un EEG con ondas de baja frecuencia (0.5 a 4 Hz) y gran amplitud, así como por la presencia de husos de sueño (11 a 16 Hz), ambos generados por la actividad sincronizada de neuronas talámicas y corticales. En forma periódica y siempre precedida de NREM, se ingresa al estado de sueño REM (Aserinsky and Kleitman, 1953). A pesar de que el sueño es profundo, el EEG es similar al de vigila (por esa razón también se denomina sueño paradójico). A su vez, se pueden observar los movimientos oculares rápidos registrados en el EOG (electrooculograma) y una baja amplitud en el EMG que refleja la atonía muscular.

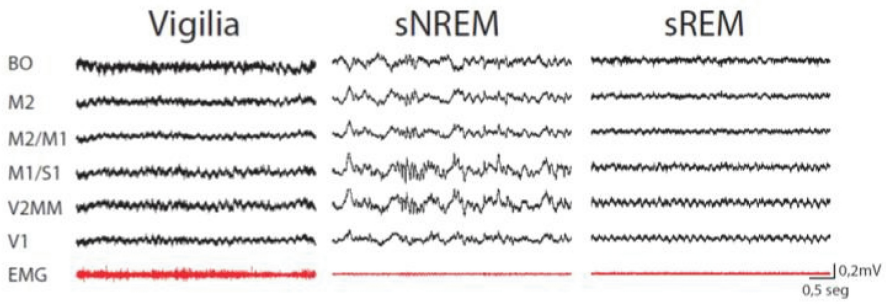


Figura 1: Registros polisomnográficos típicos de los estados de Vigilia, sueño NREM y sueño REM. En los mismos se grafican la actividad eléctrica de diferentes zonas corticales (negro) y la actividad eléctrica muscular (rojo). BO Bulbo Olfatorio, M2/M1 Cortezas Motoras; S1 Cortezas Somestésicas primarias; V2/V1 Cortezas Visuales; EMG Electromiograma del Cuello.

## 1.2. Ibogaína

La ibogaína es un alcaloide indol de origen natural (Figura 2)que se encuentra en la corteza de la raíz del arbusto Tabernanthe iboga, originario de Congo y Gabón, así como en otras plantas de la familia Apocynacea (Lavaud and Massiot, 2017). La misma posee una rica historia de uso medicinal y ceremonial en la región oeste de África. Mientras a bajas dosis era utilizado para combatir la fatiga y el hambre, dosis mas altas eran empleadas para producir visiones en condiciones de rituales debido a sus propiedades psicoactivas. Mas recientemente, la ibogaína se ha vuelto ampliamente conocida en el mundo occidental debido a sus propiedades para reducir la adicción a drogas de abuso así como también el síndrome de abstinencia generado por la interrupción en el consúmo de las mismas (Alper et al., 1999). Dichos efectos han sido confirmados en estudios preclínicos en roedores, donde se observó una disminución de la autoadministración de una variedad de drogas, como opioides (Lotsof, 1995), cocaína (Cappendijk and Dzoljic, 1993), alcohol (Rezvani et al., 1995) y nicotina (Glick et al., 1998). En los seres humanos, estas propiedades anti-adictivas se han destacado en muchos informes anecdóticos y estudios observacionales (Schenberg et al., 2014),(Brown and Alper, 2017).

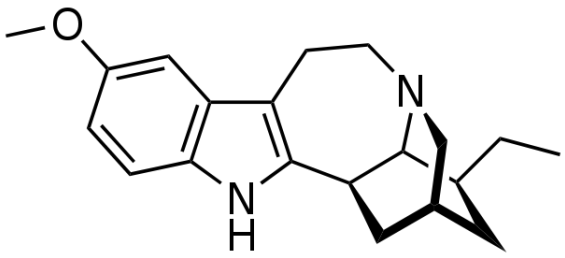


Figura 2: Estructura química de la ibogaína

## 1.3. Mecanismos de Acción

En contraste con otros tratamientos farmacológicos a la adicción, la ibogaína se diferencia en que su mecanismo de acción no involucra un solo neurotransmisor o sistema. Por el contrario, presenta afinidad por diferentes receptores a nivel del sistema nervioso central, entre los que se destaca por ser antagonista competitivo NMDA, agonista $\mu$, $\kappa$ y $\sigma$ opioide, como también por presentar afinidad por el transportador de serotonina y bloquear su recaptación (Popik et al., 1995). En relación al sistema colinérgico los resultados no se encuentran bien definidos siendo reportada tanto como agonista (Schneider and Sigg, 1957) o antagonista (Sweetnam et al., 1995a) para receptores muscarínicos y nicotínicos. Por otro lado, existe evidencia de que la ibogaína inhibe la recaptación de dopamina (Wells et al., 1999) y disminuye la liberación de dopamina en respuesta a la morfina (Pearl et al., 1996). En relación a este último punto, posee un efecto bifásico dosis dependiente sobre la descarga neuronal en un área dopaminérgica como es el área tegmental ventral (VTA) (French et al., 1996). Por último, en los últimos años se ha estudiado la acción de la ibogaína sobre diversos neuropéptidos como el GDNF y BDNF (factores de crecimientos derivados del cerebro

y de celulas gliales) en relación a los fenómenos anti-adictivos a largo plazo. Se ha encontrado que la ibogaína aumenta los niveles de GDNF a nivel de diversas estructuras del mesencéfalo relacionadas a fenómenos conductuales y de adicción (He and Ron, 2006).

Resulta interesante aclarar que varios de los sistemas mencionados previamente (serotoninérgico, dopaminérgico, colinérgico) pertenecen al sistema reticular activador ascendente, crítico para el mantenimiento de la vigilia y la generación de sueño REM (Torterolo and Vanini, 2010). Es importante destacar que estos núcleos moduladores constituyen verdaderos sistemas de proyección difusa capaces de alcanzar diversas estructuras cerebrales distantes.

## 1.4. Metabolismo

La ibogaína tiene una vida media de 1 hora en roedores (Dhahir, 1971) y 7,5 horas en humanos. A su vez es metabolizada en el tejido hepático hacia noribogaína por demetilación a través del citocromo P450. La noribogaína es detectable en el tejido cerebral 15 minutos después de la administración oral de ibogaína 50 mg/kg (Staley et al., 1996a). Esta es también farmacológicamente activa, difiriendo con la ibogaína en su mayor afinidad hacia el transportador de serotonina (SERT) y hacia los receptores opioides (Mash et al., 1995). Su vida media se estima entre 28 y 49 horas en humanos (Glue et al., 2015), mientras que en roedores no está determinada.

## 1.5. Efectos Cognitivos

La ibogaína ha sido clasificada como una droga psicodélica[2] oneirogénica por su capacidad para inducir episodios vívidos similares a los sueños durante la vigilia con ojos cerrados, sin pérdida de contacto con el medio ambiente (Naranjo, 1973). Esta actividad onírica no produce las interferencias típicas en el pensamiento, las distorsiones de identidad y la alteración del espacio-tiempo producidas por las drogas psicodélicas tradicionales (también conocidas como alucinógenos) como la dietilamida del ácido lisérgico (LSD), la mescalina y la dimetiltriptamina (DMT), clasificadas farmacológicamente como agonistas del receptor de serotonina 5-HT2A (Naranjo, 1973; Glennon, 1990; Lotsof, 1995; Nichols, 2016).

Es interesante mencionar los efectos subjetivos de acuerdo a narraciones de pacientes (Lotsof, 1995). El efecto agudo comienza entre la primera hora y tercera hora de administrada. En general es descrita como una experiencia de carácter reflexiva involucrando recuerdos de la persona en conjunto con visiones. Estas visiones difieren a las alucinaciones propias de drogas como el LSD, sino que se asemejan a las alucinaciones hipnagógicas por su similitud a los sueños. Esta es una de las razones por las cuales a la ibogaína se la refiere como un oneirogénico (del griego oneiro, que se traduce como sueño) y no como un alucinógeno.

## 1.6. Sueño e Ibogaína

Como se ha mencionado previamente se califica a la ibogaína como un oneirogénico. Sin embargo, el efecto de la ibogaína sobre W y el sueño sigue sin estar claro, existiendo solo unos pocos estudios con respecto a este tema. Un estudio en gatos describió

[2]proveniente del griego *psique* "mente" y *delos* "manfiestar, hacer visible". Este termino fue propuesto por primera vez por el psiquiatra británico Humphrey Osmond en una serie de conversaciones con el escritor Aldous Huxley en relación a la naturaleza y efectos del LSD.

que la administración de ibogaína (dosis de 2-10 mg / kg) produjo una activación del EEG que se asemeja al efecto de la estimulación eléctrica del sistema reticular activador (Schneider and Sigg, 1957). Este efecto se redujo en el modelo animal clásico de "descerebración", lo que sugiere para los efectos de la ibogaína formación reticulada tiene un papel clave. Además, estos autores demostraron que la atropina, un antagonista colinérgico muscarínico, bloquea el efecto de activación del EEG inducido por la ibogaína. Debido a este resultado, los autores sugirieron que el efecto de la ibogaína depende de la activación del sistema colinérgico. Existen también otro experimentos en los cuales se analizaron los efectos de otros alcaloides derivados de iboga en gatos implantados crónicamente (Da Costa et al., 1980; Da Costa-Rochette et al., 1981). En los mismos se encontró que el tartrato de tabernanthine y el p-chlorophenoxyacetate de tabernanthine provocaban un aumento en W y una reducción tanto del sueño NREM como del sueño REM. Sin embargo, se encontró el efecto opuesto cuando se administraron otros derivados de tabernanthine (aludidos como tartrato de metoxi-16-ibogaína y tartrato de tabernanthina-metoxi-16).

Por otro lado, existe una hipótesis que vincula directamente las propiedades antiadictivas de la ibogaína con el sueño REM, formulada por el químico francés Robert Goutarel (Goutarel et al., 1993). Según esta hipótesis, la ibogaína induciría un estado similar al sueño REM, donde la alta plasticidad neuronal promovería un re procesamiento de la información en conjunto con la formación de nuevas asociaciones. Según este modelo, durante el efecto de la ibogaína ocurriría un debilitamiento de conexiones relacionadas a las conductas y comportamientos adictivos. Aunque puramente especulativa, esta hipótesis guarda cierta correlación entre las funciones fisiológicas del sueño REM y con el estado activo del EEG inducido por la ibogaína.

## 1.7. Perspectivas para la Biología Humana

Dado el importante problema biológico y social de las adicciones resulta crítico entender como ciertas sustancias son capaces de proveer un tratamiento a estas condiciones. Específicamente, la ibogaína difiere en gran medida con los tratamientos actuales en su gran efectividad e inmediatez[3]. Por este motivo el conocimiento de los mecanismos de acción de la ibogaína podría resultar vital para el desarrollo de nuevos fármacos mas efectivos e inmediatos. A su vez, dicho proceso proveerá inevitablemente nuevos conocimientos sobre las bases reales del problema, es decir los procesos neurobiológicos subyacentes a las distintas adicciones. Por último, es importante indagar acerca de las diferencias entre las propiedades oneirofrénicas de la ibogaína y los efectos de los psicodélicos tradicionales (agonistas 5-HT2A). Esto se debe a que el factor alucinógeno ha sido el principal responsable de que este alcaloide no se haya considerado como candidato prometedor de la terapéutica hacia las adicciones.

## 1.8. Objetivos del trabajo

El objetivo principal fue caracterizar los efectos de la ibogaína sobre la vigilia y el sueño, utilizando la rata como modelo animal. Con este propósito se midieron los efectos sobre los tiempos totales, latencias, frecuencias y duraciones de los episodios de cada uno de los estados comportamentales mencionados previamente.

[3]Es interesante destacar que existen actualmente clínicas que utilizan la ibogaina como tratamiento y que han publicado sus resultados (Davis et al., 2017; Wilkins et al., 2017).

# 2. Materiales y Métodos

## 2.1. Ibogaína

La ibogaína purificada (96,4 %) fue provista por el Dr Ignacio Carrera del Departamento de Química Orgánica de la Facultad de Química. Para detalles del proceso sintético ver sección 7.1 en la página 20.

## 2.2. Animales de experimentación

Se emplearon 8 ratas Wistar adultas (270-300 g) mantenidas en un ciclo de luz / oscuridad de 12 hs (las luces se encendieron a las 07:00 h). La comida y el agua estaban disponibles libremente. Los veterinarios de la institución determinaron que los animales disponían de buena salud. Todos los procedimientos experimentales se realizaron de acuerdo con la Ley Nacional de Cuidado de Animales (Nº 18611) y con la "Guide to the care and use of laboratory animals" (8th edition, National Academy Press, Washington DC, 2010). Los protocolos experimentales fueron aprobados por el Comité de Ética de la Facultad de Medicina (CEUA) y Comisión Honoraria de Experimentación Animal (CHEA) (Registro Institucional No 070153-000409-17). Se tomaron las medidas adecuadas para minimizar el dolor, la incomodidad o el estrés de los animales, y se hicieron todos los esfuerzos para utilizar el número mínimo de animales necesarios para obtener datos científicos confiables.

## 2.3. Procedimientos quirúrgicos

Los animales fueron implantados crónicamente con electrodos para monitorear los estados de sueño y de vigilia. Empleamos procedimientos quirúrgicos similares a los de nuestros estudios previos (Benedetto et al., 2013; Cavelli et al., 2015; Cavelli et al., 2017a). La anestesia se indujo con una mezcla de ketamina-xilazina (90 mg/kg, 5 mg/kg i.p., respectivamente). La rata se colocó en un marco estereotáctico y el cráneo quedó expuesto. Para registrar el EEG, se colocaron electrodos de tornillo de acero inoxidable en el cráneo por encima de las cortezas occipitales, parietales, frontales, el bulbo olfatorio derecho y el cerebelo (electrodo de referencia), ver figura 3. Para registrar el electromiograma (EMG), se insertaron dos electrodos en el músculo del cuello. Los electrodos se soldaron en un conector de 12 pines y se fijaron en el cráneo con cemento acrílico. Al final de los procedimientos quirúrgicos, se administró un analgésico (ketoprofeno, 1 mg/kg, s.c.). Una vez que los animales se recuperaron de los procedimientos quirúrgicos, se adaptaron a la cámara de registro durante 1 semana.

## 2.4. Sesiones Experimentales

Los animales se alojaron individualmente en jaulas transparentes (40 x 30 x 20 cm) que contenían aserrín en una habitación con temperatura controlada (21-24°C), con agua y comida *ad líbitum*. Las sesiones experimentales se llevaron a cabo durante el período de luz, entre las 10 AM y las 4 PM, en una cámara atenuada tanto acústica como eléctricamente. Los registros se realizaron a través de un conector giratorio, para permitir que las ratas se movieran libremente dentro de la caja de registro. Los datos polisomnográficos se adquirieron y almacenaron en una computadora para su posterior análisis, utilizando el *hardware* y *software* Spike 2 (CED, Cambridge, Reino Unido). Las señales crudas fueron amplicadas (1000x) y digitalizadas a 1024 Hz utilizando

una tarjeta conversora Analógica-Digital de 16 bits. Los estados de sueño y vigilia se determinaron en épocas de 10 segundos. W se definió en base a la presencia de ondas rápidas de bajo voltaje en la corteza frontal, un ritmo theta mixto (4-7 Hz) en las cortezas parietales y una actividad EMG relativamente alta. Sueño ligero (LS) por la presencia de ondas corticales lentas de gran amplitud interrumpidas por ondas rápidas de bajo voltaje. El sueño lento profundo (SWS) se definió por la presencia de ondas lentas de gran amplitud continuas y husos de sueño en las cortezas frontales, parietales y occipitales asociadas con una amplitud del EMG reducida; mientras que el sueño REM por la presencia de ondas frontales rápidas de bajo voltaje, un ritmo theta regular en la corteza occipital y un EMG silente a excepción de twitches ocasionales. Se analizó el tiempo total de sueño para cada uno de los estados definidos previamente (W, LS, SWS y REM), así como la duración y el número de episodios durante un período de registro de 6 hs. Las latencias del sueño también fueron evaluadas. Además, el tiempo transcurrido en cada estado se analizó por separado en bloques de 2 hs (0-2, 2-4 y 4-6 hs) de modo similar a (Monti et al., 2015). Para estudiar el efecto de la ibogaína sobre el sueño y la vigilia, al comienzo de los registros, cada rata recibió ibogaína 20 mg/kg (I20), 40 mg/kg (I40) o vehículo (solución salina) por via intraperitoneal en días diferentes en un orden contrabalanceado; el período de lavado entre las dosis fue de 3 días. Estas dosis se han usado ampliamente en estudios de adicción preclínica (Glick et al., 1991; Cappendijk and Dzoljic, 1993).

## 2.5. Análisis de datos

Todos los valores se presentan como la media ± error estandar. El diseño experimental para el análisis del sueño fue un diseño pareado, donde se evaluó la significación estadística de las diferencias entre grupos (ibogaína 0, 20 y 40 mg/kg) utilizando el análisis de varianza (ANOVA) de medidas repetidas y *post hoc* de Bonferroni (Monti et al., 2015). Cuando los criterios de esfericidad (probados por la prueba de Mauchly) no se cumplieron, se aplicó la corrección Greenhouse-Geisser. La significancia estadística se estableció $p < 0.05$.

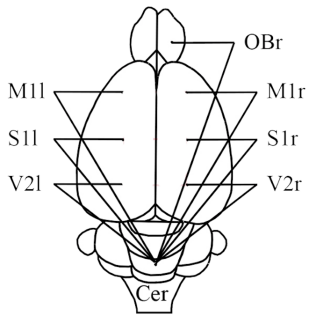


Figura 3: Ubicación espacial de los electrodos de registro. OB Bulbo Olfatorio; M1 Corteza Motora Primaria; S1 Corteza Somestesica Primaria; V2 Corteza Visual Secundaria (r y l denotan cortezas derechas e izquierdas respectivamente).

# 3. Resultados

## 3.1. Efecto de la ibogaína sobre los tiempos totales de Vigilia y Sueño

La Figura 4 muestra un hipnograma y un espectrograma de un animal representativo después de la administración de solución salina, I20 e I40. Comparado con el control, I20 [F (1.1,8.3) = 10.7, p <0.01] e I40 [F (1.1,8.3) = 10.7, p <0.05] aumentaron el tiempo pasado en W (Figura 4 y Tabla 1 ). Este efecto fue acompañado por una disminución en el tiempo de SWS, I20 [F (2,14) = 14.7, p <0,01], I40 [F (2,14) = 14.7, p = 0,01]. Además, la cantidad total de sueño REM disminuyó en animales tratados con I20 [F (2,14) = 19.3, p <0.01] e I40 [F (2,14) = 19.3, p <0.005]. No se observaron diferencias en la cantidad total de LS.

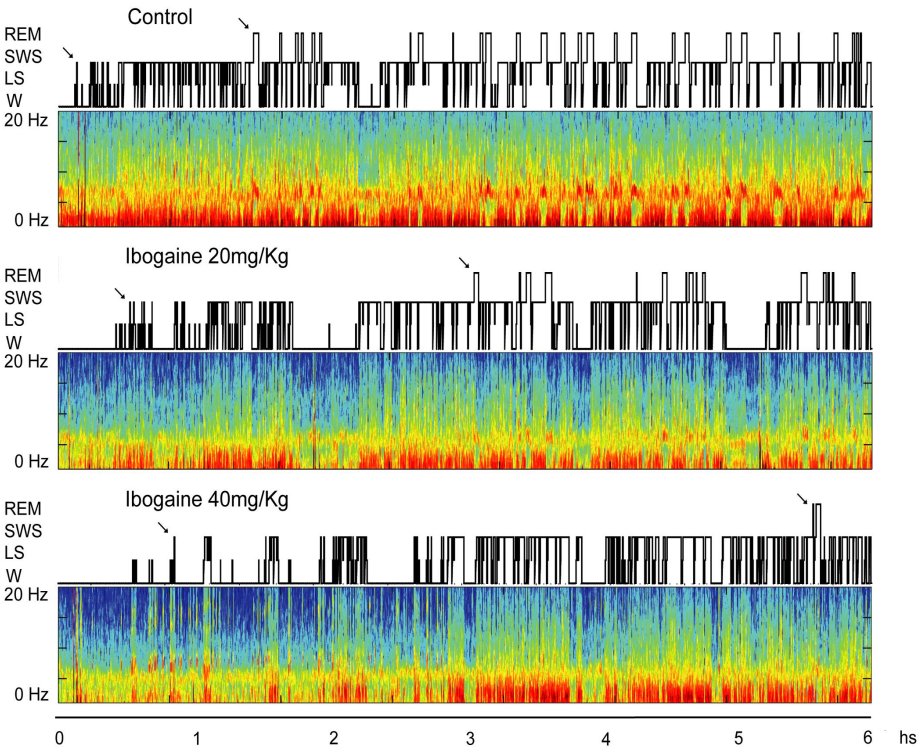


Figura 4: Hipnogramas y espectrogramas (0.1-20 Hz) de un animal representativo tras la administración de salino, I20 e I40. Las flechas indican el primer episodio de SWS y de REM. Tomado de (Gonzalez et al., 2018).

### 3.2. Efecto de la ibogaína sobre la duración, el número de episodios y las latencias al sueño

Al considerar la duración y el número de episodios (Tabla 1), encontramos que, en comparación con el control, hubo un aumento significativo en la duración de los episodios de W individuales después de I20 [F (1.1, 7.9) = 6.4, p <0.05], y una disminución en la duración de los episodios de SWS para I40 [F (2,14) = 9.5, p <0.005]. Con respecto al sueño REM, ambas dosis de ibogaína redujeron el número total de episodios [F (1.2,8.5) = 10.5; p <0.05 para I20 e I40] sin afectar la duración de los mismos. Finalmente, la latencia del sueño REM aumentó después de la administración de I40 [F (2,14) = 9.6, p <0,05] (Tabla 1), mientras que la latencia para LS y SWS no se vio afectada.

### 3.3. Resultados de los bloques individuales

Los efectos de la ibogaína también se analizaron en bloques de 2 hs (Figura 5). Comparado con el control, el tiempo de W aumentó significativamente para ambas dosis en las primeras 2 hs del registro [F (2,14) = 9.1, p <0,05 para I20 e I40]. Este incremento fue acompañado por una disminución en SWS [F (2,14) = 10.2, p <0.05 para I20, y p <0.01 para I40] y sueño REM [F (2,14) = 17.8, p <0.05 para I20 y p = 0.001 para I40] sin ningún cambio apreciable en LS. Dentro de las 2 hs siguientes, se observó una disminución en el sueño REM después de I40 [F (2,14) = 8.7, p <0.05], mientras que en las últimas 2 hs, tanto I20 como I40 disminuyeron el tiempo de sueño REM [F (1.1, 7.8) = 8.3, p <0,005 para I20 y p <0,05 para I40].

## 4. Discusión

En el presente estudio, observamos que la administración de ibogaína 20 y 40 mg/kg produce un efecto robusto sobre el sueño y la vigilia, promoviendo un estado de vigilia que se acompaña de una supresión duradera del sueño REM. Como se encuentra bien establecido que la ibogaína se metaboliza rápidamente a su metabolito de larga duración noribogaína, ambas sustancias deben tenerse en cuenta para explicar los hallazgos de este estudio. En acuerdo con trabajos anteriores que utilizaban la via de administracion intraperitoneal en ratas (Baumann et al., 2001a), la concentración de ibogaína en sangre disminuye rápidamente en la primera hora mientras que la concentración de noribogaína es máxima a las 2.4 horas y dura por lo menos hasta 24 horas.

La administración de ibogaína tuvo un efecto activador, promoviendo la vigilia; acompañado por una disminución en la cantidad total de SWS y sueño REM. Si bien los efectos sobre W y SWS se observaron solo en las primeras 2 hs, los efectos sobre el sueño REM persistieron durante la totalidad del tiempo de registro. Estos resultados son reminiscentes a estudios observacionales en humanos, donde la administración de ibogaína en dosis múltiples produjo dificultades tanto en el inicio como en el mantenimiento del sueño inmediatamente después de administrada (Wilkins et al., 2017). Además el efecto de promoción de W, aparece también en un reporte anterior en gatos (Schneider and Sigg, 1957), lo que sugiere que la ibogaína induce W en ratas, gatos y probablemente en humanos.

| | Control | Ibogaine 20 mg/kg | Ibogaine 40 mg/kg |
|---|---|---|---|
| **Wakefulness** | | | |
| Total duration (min) | 95.1 ± 7.8 | 135.5 ± 9.8* | 182.6 ± 26.6* |
| Number of episodes | 118.0 ± 8.9 | 130.8 ± 8.1 | 127.1 ± 10.4 |
| Episodes duration (min) | 0.8 ± 0.0 | 1.0 ± 0.1* | 1.5 ± 0.2 |
| **Light sleep (LS)** | | | |
| Total duration (min) | 32.6 ± 2.6 | 39.4 ± 3.0 | 37.6 ± 4.3 |
| Number of episodes | 152.6 ± 3.4 | 173.7 ± 4.4 | 163.2 ± 5.4 |
| Episodes duration (min) | 0.21 ± 0.0 | 0.2 ± 0.0 | 0.22 ± 0.0 |
| **Slow wave sleep (SWS)** | | | |
| Total duration (min) | 197.8 ± 8.0 | 162.3 ± 7.3* | 127.4 ± 19.6* |
| Number of episodes | 141.5 ± 7.4 | 152.5 ± 13.7 | 124.8 ± 7.8 |
| Episodes duration (min) | 1.4 ± 0.9 | 1.1 ± 0.8 | 1.0 ± 0.8* |
| Latency | 9.1 ± 1.7 | 21.8 ± 3.6 | 53.2 ± 14.9 |
| **REM sleep** | | | |
| Total duration (min) | 33.6 ± 2.5 | 22.0 ± 2.8* | 11.5 ± 3.7* |
| Number of episodes | 25.1 ± 2.3 | 19.6 ± 2.6* | 11.8 ± 4.7* |
| Episodes duration (min) | 1.3 ± 0.0 | 1.1 ± 0.1 | 0.8 ± 0.2 |
| Latency (min) | 72.5 ± 2.7 | 137.1 ± 24.8 | 229.8 ± 43.4* |

Tabla 1: Efecto de la administracion i.p de ibogaína sobre los parametros de Vigilia y Sueño. En la tabla se muestra la media y el error estandard de los datos observados. * Denotan las diferencias significativas con respecto al control, utilizando ANOVA de medidas repetidas, seguidas de la prueba *post-hoc* de Bonferroni ($p < 0.05$). Tomado de (Gonzalez et al., 2018).

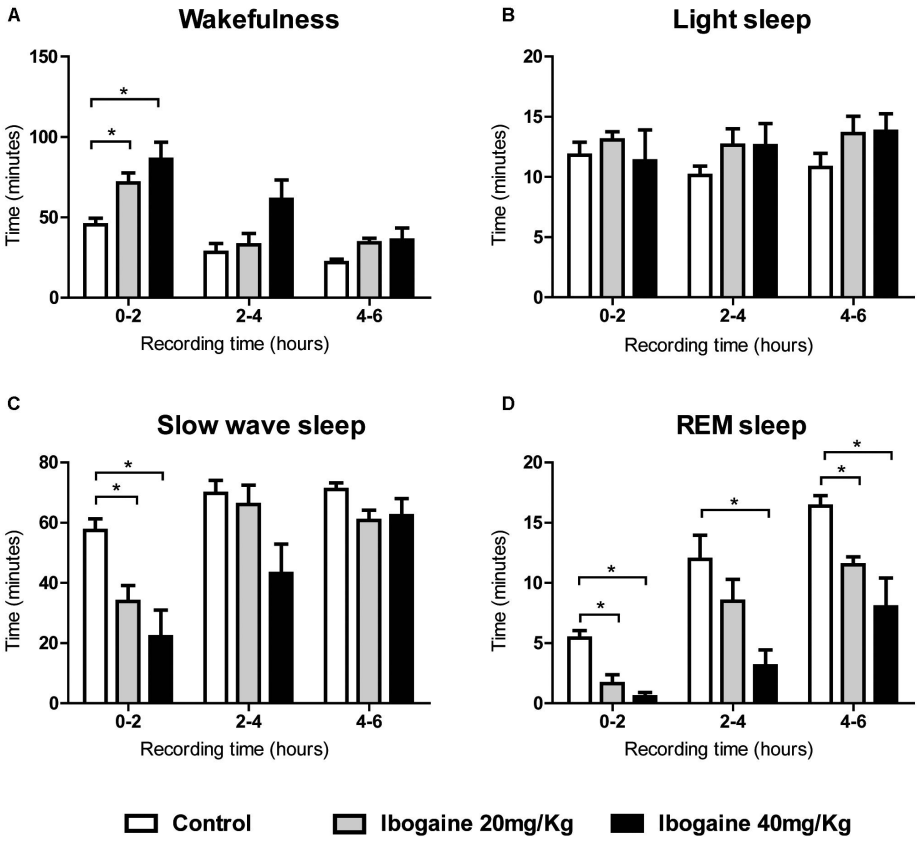


Figura 5: Efecto de la administracion i.p de ibogaína sobre W,LS,SWS y REM. En la Figura se muestra la media y el error estandard de los datos observados. * Denotan las diferencias significativas con respecto al control, utilizando ANOVA de medidas repetidas, seguidas de la prueba *post-hoc* de Bonferroni( $p < 0.05$). Tomado de (Gonzalez et al., 2018).

Curiosamente, se ha informado de un impacto similar en la arquitectura del sueño para los psicodélicos tradicionales (agonistas de 5-HT2A), como el LSD (también un agonista del receptor 5-HT2C) y 2,5-dimetoxi-4-yodoanfetamina (DOI, también un agonista de 5-HT2C) (Depoortere and Loew, 1971; Monti and Jantos, 2006). El tratamiento crónico con LSD en ratas promueve un aumento de W y una reducción en el sueño SWS y REM. Similar a la ibogaína, el efecto promotor de W fue más prominente durante la primera hora, mientras que desapareció después de las 4 hs. Los autores también encontraron cambios cualitativos en el sueño REM, informando un aumento en los episodios fásicos, así como un aumento en los movimientos oculares rápidos. La administración subcutánea de DOI también aumenta W y disminuye el sueño SWS y REM. En conjunto, estos resultados sugieren que la ibogaína y los psicodélicos tradicionales inducen efectos similares en la arquitectura del sueño. Con respecto a los antagonistas selectivos de los receptores 5-HT2A y 5-HT2C, se encontró que su administración promueve SWS; mientras que sorprendentemente disminuye el tiempo de sueño REM (Monti and Jantos, 2006; Monti et al., 2018). Estos resultados inesperados no han sido explicados aún.

Dado que los sueños son la contraparte cognitiva del sueño REM (aunque también pueden ocurrir sueños bajo el sueño NREM), la supresión del sueño REM de larga duración inducida por la administración de ibogaína parece a primera vista contraria a sus propiedades oneirogénicas mencionadas anteriormente. Sin embargo, este puede no ser el caso, ya que un análisis cuantitativo del EEG durante W podría proporcionar evidencia de un patrón de W alterado. Por ejemplo, la W inducida por ibogaína podria presentar una disminución en la coherencia de la banda gamma, siendo esta una firma electrofisiológica bien conocida del sueño REM (Castro et al., 2013; Cavelli et al., 2015; Cavelli et al., 2017b). En otras palabras, este estado W inducido farmacológicamente podría tener sutiles rasgos electrofisiológicos del sueño REM que podrían explicar el efecto cognitivo oneirogénico del fármaco. Con el objetivo de responder a esta pregunta, un análisis cuantitativo del EEG (potencia, coherencia, co-modulación, entropía) está en proceso. Además, este tipo de análisis sería útil para comparar la calidad de W producida por ibogaína con los psicodélicos tradicionales.

Con el fin de evaluar la calidad de la vigilia inducida por la ibogaína se llevaron a cabo análisis detallados de la actividad locomotora, realizados en el laboratorio de la Dra. Cecilia Scorza. Para detalles de dichos resultados ver la sección 7.1 en la pagina 20. Con respecto al comportamiento motor, se encontró una actividad locomotora total más alta después de la administración de I20 sugiriendo una respuesta animal más vigilante. Este efecto estimulante está de acuerdo con los hallazgos previos que mostraron que las dosis 1 y 10 mg / kg i.v. promovieron un aumento dosis dependiente en la actividad locomotora en ratas (Baumann et al., 2001b). Por el contrario, la administración de I40 no mostró un aumento sustancial de la actividad locomotora, produciendo comportamientos similares al síndrome de la serotonina, tales como temblor y postura plana del cuerpo, principalmente durante la primera parte de la sesión de registro. Tomados en conjunto, estos resultados indican claramente que I40 induce un tipo de W que es diferente a la producida por la dosis más baja. Estos resultados se asemejan a la experiencia subjetiva de los nativos de Congo y Gabón que utilizaban dosis bajas de la corteza de la raíz de iboga como un potente estimulante para combatir la fatiga y el cansancio, mientras que utilizaban dosis mayores para producir visiones en entornos de rituales (Schneider and Sigg, 1957; Pope, 1969).

¿Cuáles son los mecanismos subyacentes responsables de los efectos supresores del sueño REM y promotores de la vigilia? Los experimentos en sinaptosomas han demostrado que la ibogaína inhibe la recaptación de serotonina, lo que aumenta los niveles

sinápticos de este neurotransmisor (Wells et al., 1999). Además, Wei y colaboradores (1998)(Wei et al., 1998)demostraron que la ibogaína provocaba un gran aumento en los niveles de serotonina (hasta 25 veces en el Nucleus Accumbens, NAC y 10 veces en el cuerpo estriado, STR), mientras que la noribogaína producía un aumento moderado (hasta ocho veces en NAC y cinco veces en STR). Por el contrario, otros autores mostraron que la noribogaína era más potente en el aumento de los niveles de serotonina en el NAC que la ibogaína, lo que se correlaciona con la capacidad de ambos compuestos para inhibir SERT (IC50 de 3.85 y 0.18 $\mu$M para ibogaína y noribogaína, respectivamente) (Baumann et al., 2001b). Estos autores sugirieron que la ibogaína y la noribogaína son inhibidores de la recaptación de serotonina con un mecanismo de acción similar a la fluoxetina. La serotonina aumenta la vigilia y suprime la generación de sueño REM (Oniani and Akhvlediani, 1988; Monti and Jantos, 2005). Por lo tanto, la capacidad de la ibogaína y la noribogaína para aumentar la concentración de serotonina sináptica podría explicar el incremento en el tiempo de W, así como el efecto supresor REM de larga duración. El hecho de que la mayoría de las drogas antidepresivas compartan este efecto de supresión del sueño REM (Palagini et al., 2012), insinúa que la ibogaína también podría tener propiedades antidepresivas según lo sugerido por los trabajos en seres humanos (Mash et al., 2000).

Por otro lado el temblor y la postura corporal plana inducidas por la ibogaína (ver sección 7.1) sugieren una interacción con la transmisión serotoninergica. Sin embargo, se ha postulado que un mecanismo serotoninérgico no puede estar involucrado en los efectos locomotores de la ibogaína, ya que según algunos resultados, la noribogaína (que no es tremorogénica en ratas) es más potente en el aumento de los niveles de serotonina que la ibogaína (Baumann et al., 2001b). De esta manera, se especula que los receptores sigma o NMDA también podrían explicar estos comportamientos (ya que la noribogaína tiene menor afinidad por estos sitios). En relación a la interacción de la ibogaina con el receptor 5-HT2A, diversos estudios sugieren una baja interaccion por dicho subtipo de receptor. Los datos farmacológicos favorecen esta diferencia, mientras que los alucinógenos interactúan con el receptor 5-HT2A en el rango nanomolar, la afinidad de la ibogaína para este receptor está en el rango micromolar (Ki 4.8-92.5 $\mu$M según el estudio) (Repke et al., 1994; Sweetnam et al., 1995b; Helsley et al., 1998; Glick et al., 1999) o insignificante (Deecher et al., 1992; Staley et al., 1996b). Un signo característico generado por los agonistas 5-HT2A es la inducción de el comportamiento que se conoce como "head shake response", en este sentido no se describieron estos comportamientos para ninguna de las dosis empledas en este trabajo (ver sección 7.1). Como se mencionó anteriormente, este comportamiento se ve agravado por la administración sistémica de los agonistas del receptor 5-HT2A (como los psicodélicos clásicos). Esto constituye una diferencia de comportamiento entre los animales tratados con estos compuestos (LSD, DOI, etc.) frente a la ibogaína, que se considera un psicodélico no tradicional. Por último, esta diferencia también se ve respaldada por las diferencias entre las experiencias subjetivas en humanos donde la ibogaína no produce las interferencias típicas en el pensamiento, las distorsiones de identidad y la alteración espacio-temporal producida por las drogas psicodélicas tradicionales (Naranjo, 1973).

También se ha propuesto que la activación de las vías colinérgicas debería estar involucrada en los efectos producidos por la ibogaína (Schneider and Sigg, 1957). En este sentido, las neuronas colinérgicas del mesencéfalo y cerebro anterior basal están involucradas en la generación y mantenimiento de W (Torterolo et al., 2016). Por lo tanto, es probable que mediante la modulación de estos sistemas neuroquímicos, la ibogaína pueda promover la vigilia y suprimir el sueño.

Sin embargo, debido a la compleja farmacología de la ibogaína, las posibles inter-

acciones entre los neurotransmisores previamente mencionados, así como también los efectos aún desconocidos de la ibogaína sobre las neuronas que promueven el sueño REM como la hormona concentradora de melanina (MCH), deben tenerse en cuenta al interpretar estos resultados (Torterolo et al., 2011; Monti et al., 2013). Otra posibilidad es que el aumento en W podría ser causado por algún efecto inespecífico, como irritación o dolor. En este sentido, no observamos ningún comportamiento que sugieriera este tipo de efecto. De hecho, es interesante considerar que existe evidencia de la ibogaína como un agente antinociceptivo (Olney, 1995; Olney, 1997). Además, tanto la ibogaína como la noribogaína potencian la antinocicepción inducida por la morfina (Bagal et al., 1996) y a nuestro entender, no existen estudios observacionales que informaran dolor o inflamación después de la administración de ibogaína en humanos.

Por último, al considerar los resultados observados en cada bloque de 2 hs, planteamos la hipótesis de que los diferentes efectos observados a lo largo de todo el tiempo de registro podrían atribuirse no solo a la misma ibogaína, sino también a su principal metabolito, la noribogaína. Como se mencionó anteriormente, de acuerdo con informes anteriores que usan administración i.p. en ratas, la concentración de ibogaína en sangre disminuye rápidamente en la primera hora (con una T-max de aproximadamente 0.1 h), mientras que la noribogaína es detectable en sangre hasta 24 hs después de la administración de ibogaína (con una T-max de aproximadamente 2.4 hs) (Baumann et al., 2001b). Por lo tanto, el aumento de vigilia encontrado en el primer bloque de 2 hs podría correlacionarse con la concentración máxima de ibogaína en sangre, mientras que la supresión de REM extendida a lo largo de toda el periodo de registro podría atribuirse a la noribogaína de larga duración. Se necesitan más experimentos para confirmar esta hipótesis.

# 5. Conclusiones

En este estudio, observamos que la administración intraperitoneal de ibogaína en ratas produjo un aumento de la vigilia, una disminución en SWS junto con una supresión robusta del sueño REM. Por lo tanto, dado que la ibogaína se considera un psicodélico oneirogénico, el siguiente paso sería analizar las características electroencefalográficas específicas de la W inducida farmacológicamente, como el espectro de potencia y la coherencia entre las diferentes áreas corticales. Este tipo de análisis podría proporcionar información adicional sobre la contraparte cognitiva de nuestros resultados.

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# 7. Anexos

## 7.1. Ibogaine Acute Administration in Rats Promotes Wakefulness, Long-Lasting REM Sleep Suppression, and a Distinctive Motor Profile

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# Ibogaine Acute Administration in Rats Promotes Wakefulness, Long-Lasting REM Sleep Suppression, and a Distinctive Motor Profile

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Ibogaine is a potent psychedelic alkaloid that has been the focus of intense research because of its intriguing anti-addictive properties. According to anecdotic reports, ibogaine has been originally classified as an oneirogenic psychedelic; i.e., induces a dream-like cognitive activity while awake. However, the effects of ibogaine administration on wakefulness (W) and sleep have not been thoroughly assessed. The main aim of our study was to characterize the acute effects of ibogaine administration on W and sleep. For this purpose, polysomnographic recordings on chronically prepared rats were performed in the light phase during 6 h. Animals were treated with ibogaine (20 and 40 mg/kg) or vehicle, immediately before the beginning of the recordings. Furthermore, in order to evaluate associated motor behaviors during the W period, a different group of animals was tested for 2 h after ibogaine treatment on an open field with video-tracking software. Compared to control, animals treated with ibogaine showed an increase in time spent in W. This effect was accompanied by a decrease in slow wave sleep (SWS) and rapid-eye movements (REM) sleep time. REM sleep latency was significantly increased in animals treated with the higher ibogaine dose. While the effects on W and SWS were observed during the first 2 h of recordings, the decrement in REM sleep time was observed throughout the recording time. Accordingly, ibogaine treatment with the lower dose promoted an increase on locomotion, while tremor and flat body posture were observed only with the higher dose in a time-dependent manner. In contrast, head shake response, a behavior which has been associated in rats with the $5HT_{2A}$ receptor activation by hallucinogens, was not modified. We conclude that ibogaine promotes a waking state that is accompanied by a robust and long-lasting REM sleep suppression. In addition, it produces a dose-dependent unusual motor profile along with other serotonin-related behaviors. Since ibogaine is metabolized to produce noribogaine, further experiments are needed to elucidate if the metabolite and/or the parent drug produced these effects.

**Keywords: REM sleep, wakefulness, ibogaine, psychedelics, hallucinogens**

## INTRODUCTION

Ibogaine is a natural occurring indole alkaloid found in the root bark of the shrub *Tabernanthe iboga*, originally from Congo and Gabon, as well as in other plants of the Apocynaceae family (Lavaud and Massiot, 2017). It has become widely known in the western world because of its claimed properties to reduce addiction to drugs of abuse and craving (Alper et al., 1999). These effects have been confirmed in pre-clinical studies in rodents, where ibogaine decreases self-administration of a variety of drugs such as opioids (Lotsof, 1995), cocaine (Cappendijk and Dzoljic, 1993), alcohol (Rezvani et al., 1995), and nicotine (Glick et al., 1998). In humans, the reduction of addiction and craving by ibogaine has been highlighted in many anecdotal reports and observational studies (Schenberg et al., 2014; Brown and Alper, 2017).

Ibogaine has been classified as an oneirogenic psychedelic drug for its ability to induce vivid dream-like episodes while awake with eyes closed, without loss of contact with the environment (Naranjo, 1973). This dream-like activity does not produce the typical interferences in thinking, identity distortions, and space–time alteration produced by the traditional psychedelics drugs (also known as hallucinogens) such as lysergic acid diethylamide (LSD), mescaline, and dimethyltryptamine (DMT), which are pharmacologically classified as 5-$HT_{2A}$ receptor agonists (Naranjo, 1973; Glennon, 1990; Lotsof, 1995; Nichols, 2016). However, the effect of ibogaine on wakefulness (W) and sleep remains unclear, existing only a few early studies regarding this issue. An early report in cats described that the administration of ibogaine (2–10 mg/kg doses) produced an activation of the electroencephalogram (EEG) that resembles the effect of the electrical stimulation of the activating reticular system (Schneider and Sigg, 1957). This effect was reduced in the classical "decerebrate" animal model, suggesting that the reticular formation plays a key role in the ibogaine effects. Moreover, they demonstrated that atropine, a muscarinic cholinergic antagonist, blocked the EEG-activating effect induced by ibogaine. Because of this result, the authors suggested that ibogaine effect depends on the activation of the cholinergic system. Da Costa et al. (1980), Da Costa-Rochette et al. (1981) analyzed the effects of others iboga alkaloids on chronically implanted cats. They found that tabernanthine tartrate and tabernanthine *p*-chlorophenoxyacetate provoked an increase in W and a reduction of both slow wave sleep (SWS) as well as rapid-eye movements (REM) sleep. However, the opposite effect was found when other tabernanthine derivatives (claimed as methoxy-16 ibogaine tartrate and methoxy-16 tabernanthine tartrate) were administered (Da Costa et al., 1980; Da Costa-Rochette et al., 1981).

When considering the behavioral responses induced by ibogaine in animal models, different effects have been reported depending on the dose, time points assayed, and length of the recordings. In one of the early reports in cats, it has been described that ibogaine administration (2–10 mg/kg) immediately produced an unusual excitatory effect that evolved into reactions of rage and fear (Schneider and Sigg, 1957). A more recent study in rats showed that ibogaine (1 and 10 mg/kg, i.v.) promoted a dose-dependent increase in locomotor activity during 30 min after administration (Baumann et al., 2001a). For higher doses [10–40 mg/kg, intraperitoneal (i.p.)], ibogaine produced deleterious effects in the vestibular function and a dose-dependent reduction in the detection of sensory stimuli in rats (Kesner, 1995). In addition, rats treated with 30 and 40 mg/kg were very inactive and appeared to be in a state of "suspension" (Kesner, 1995). These facts resemble subjective reports in humans, where ibogaine (4–5 mg/kg) promotes the desire to lie down because of a loss of equilibrium while trying to walk and directs the attention inwards (Naranjo, 2016). Previous studies also demonstrated that during the first 3–4 h after administration in animals, ibogaine (30–40 mg/kg or higher doses) produced serotonin syndrome-like behaviors such as tremor, piloerection, flat body posture, and forepaw tapping (Schneider and Sigg, 1957; Glick et al., 1994; Pearl et al., 1997; Baumann et al., 2001a; Haberzettl et al., 2013). It is well known that hallucinogens induce paroxysmal rotational movement of the head in rodents, that is mediated by 5-$HT_{2A}$ receptor activation (Halberstadt et al., 2011; Nichols, 2016). This behavior is called head twitch response in mice and head shake response (HSR) in rats (Corne and Pickering, 1967; Yamamoto and Ueki, 1975; Bedard and Pycock, 1977; Halberstadt et al., 2011). To the best of our knowledge, no previous studies explored if ibogaine promotes this behavior in rodents.

The main aim of the present study was to characterize ibogaine effects on sleep and W using rat as a model system. For this purpose, we performed polysomnographic recordings in chronically prepared rats and studied the acute effects of ibogaine, at doses that have been previously employed in drug self-administration studies (20 and 40 mg/kg). In addition, in order to analyze the animal behavior during the waking state, we characterized the motor effects induced by the same doses of ibogaine in naive animals, using an open-field (OF) assay.

## MATERIALS AND METHODS

### Ibogaine

Total iboga alkaloid extract from the root bark of *T. iboga* was obtained from IbogaWorld and purified as follows. The material was suspended in aqueous 10% NaOH solution, which was extracted with ethyl acetate (4 × 200 ml). The combined organic layers were dried with $Na_2SO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography ($SiO_2$, $CH_2Cl_2$:MeOH 9:1 + 0.1% $NH_4OH$). The obtained free base was further crystallized from ethanol. Ibogaine HCl was prepared dissolving the free base in dried acetone under Argon atmosphere and the equivalent amount of HCl (aq, 36%) was added. Ibogaine hydrochloride was filtered, washed with cold acetone, dried under vacuum, and characterized by $^1$H- and $^{13}$C-NMR (see Supplementary Materials for details). Purity was determined as 96.4% by GC–MS (see Supplementary Materials for details). Dissolution of ibogaine-HCl to prepare the samples for i.p.

injection was carried out using warm saline that was previously degassed by nitrogen bubbling.

## Experimental Animals

Wistar adult rats were maintained on a 12-h light/dark cycle (lights on at 07.00 h) and housed four–six per cage before behavioral testing. Food and water were freely available. Twenty-six animals (270–300 g) were used for all performed studies: eight animals were used for sleep recordings and 18 rats were used for the evaluation of the motor activity. The animals were determined to be in good health by veterinarians of the institution. All experimental procedures were conducted in agreement with the National Animal Care Law (No. 18611) and with the "Guide to the care and use of laboratory animals" (8th edition, National Academy Press, Washington DC, 2010). Furthermore, the Institutional Animal Care Committee approved the experimental procedures. Adequate measures were taken to minimize pain, discomfort, or stress of the animals, and all efforts were made to use the minimal number of animals necessary to obtain reliable scientific data.

## Surgical Procedures

Eight animals selected for sleep experiments were chronically implanted with electrodes to monitor the states of sleep and W. We employed similar surgical procedures as in our previous studies (Benedetto et al., 2013; Cavelli et al., 2015, 2017b). Anesthesia was induced with a mixture of ketamine–xylazine (90 mg/kg; 5 mg/kg i.p., respectively). The rat was positioned in a stereotaxic frame and the skull was exposed. To record the EEG, stainless steel screw electrodes were placed on the skull above frontal, parietal, occipital cortices (bilateral), the right olfactory bulb, and cerebellum (reference electrode).

To record the electromyogram (EMG), two electrodes were inserted into the neck muscle. The electrodes were soldered into a 12-pin socket and fixed onto the skull with acrylic cement. At the end of the surgical procedures, an analgesic (Ketoprofen, 1 mg/kg, s.c.) was administered. After the animals had recovered from the preceding surgical procedures, they were adapted to the recording chamber for 1 week.

## Experimental Sessions

### Sleep Recordings

Animals were housed individually in transparent cages (40 × 30 × 20 cm) containing wood shaving material in a temperature-controlled (21–24°C) room, with water and food *ad libitum*. Experimental sessions were conducted during the light period, between 10 AM and 4 PM in a sound-attenuated chamber with Faraday shield. The recordings were performed through a rotating connector, to allow the rats to move freely within the recording box.

Polysomnographic data were acquired and stored in a computer for further analysis using Spike 2 software (CED, Cambridge, United Kingdom). The states of sleep and W were determined in 10 s epochs. W was defined as low voltage fast waves in frontal cortex, a mixed theta rhythm (4–7 Hz) in occipital cortex, and relatively high EMG activity. Light sleep (LS) as high voltage slow cortical waves interrupted by low voltage fast EEG activity. SWS was defined as continuous high amplitude slow waves and sleep spindles in frontal, parietal, and occipital cortices associated with a reduced EMG amplitude; while REM sleep as low voltage fast frontal waves, a regular theta rhythm in the occipital cortex, and a silent EMG except for occasional twitches. Total time spent in W, LS, SWS, and REM sleep, as well as the duration and the number of episodes over a 6 h recording period was analyzed. Sleep latencies were also evaluated. Besides, the time spent in each state was analyzed separately in blocks of 2 h (0–2, 2–4, and 4–6 h) (Monti et al., 2015).

In order to study the effect of ibogaine on sleep and W, at the beginning of the recordings each rat received ibogaine 20 mg/kg ($I_{20}$), 40 mg/kg ($I_{40}$), or vehicle (saline) i.p., in different days in a counterbalance order; the wash-out period between doses was 3 days. These doses have been extensively used in preclinical addiction studies (Glick et al., 1991, 1992; Cappendijk and Dzoljic, 1993).

### Motor Behavior

Eighteen naive (not operated) rats were used in these experiments. Animals were brought to the experimental room in their home cages, identified, and weighed prior to the behavioral test. An OF apparatus consisting of a square area (45 cm wide × 45 cm long × 40 cm high) with transparent plastic walls indirectly illuminated (35 luxes) to avoid reflection and shadows were employed. The OF was placed in a quiet experimental room with controlled temperature (22 ± 2°C). As rats were not habituated to the OF before drug or vehicle administration, novelty-induced motor activity was automatically recorded by a camera connected to a computer equipped with the Ethovision XT 12.0 software (Noldus, Netherlands) located above the OF. Using this video tracking software, we specifically measured the total distance traveled in meters (m) during 120 min (5 min bin), starting immediately after the drug or vehicle administration. Animals were randomly assigned to different experimental groups, where each animal received $I_{20}$, $I_{40}$, or saline ($n$ = 6 per group), and were used only once. Specific behaviors were assessed by a trained investigator every 30 min during 2 h after ibogaine administration. Each evaluation session lasted 5 min. The number of rearings was taken as an index of the vertical exploratory behavior to evaluate the animal habituation to the environment. Serotonin syndrome-like continuous behaviors such as tremor, flat body posture, piloerection, hind limb abduction, and Straub tail (Haberzettl et al., 2013) were scored using a graded scale: 0, absent; 1, equivocal; 2, present; and 3, intense (Spanos and Yamamoto, 1989; Reyes-Parada et al., 1996; Baumann et al., 2001b). In the case of forepaw treading (an intermittent behavior), an additive score of 1 was given every time the animal displayed this conduct. However, to allow a comparison with the continuous behaviors, a score of 5 (five times the animal displayed a FPT behavior) was considered as intense (3, in the abovementioned scale). Finally, the number of HSR defined as short and firm movement of the head in any direction was also recorded (Haberzettl et al., 2014).

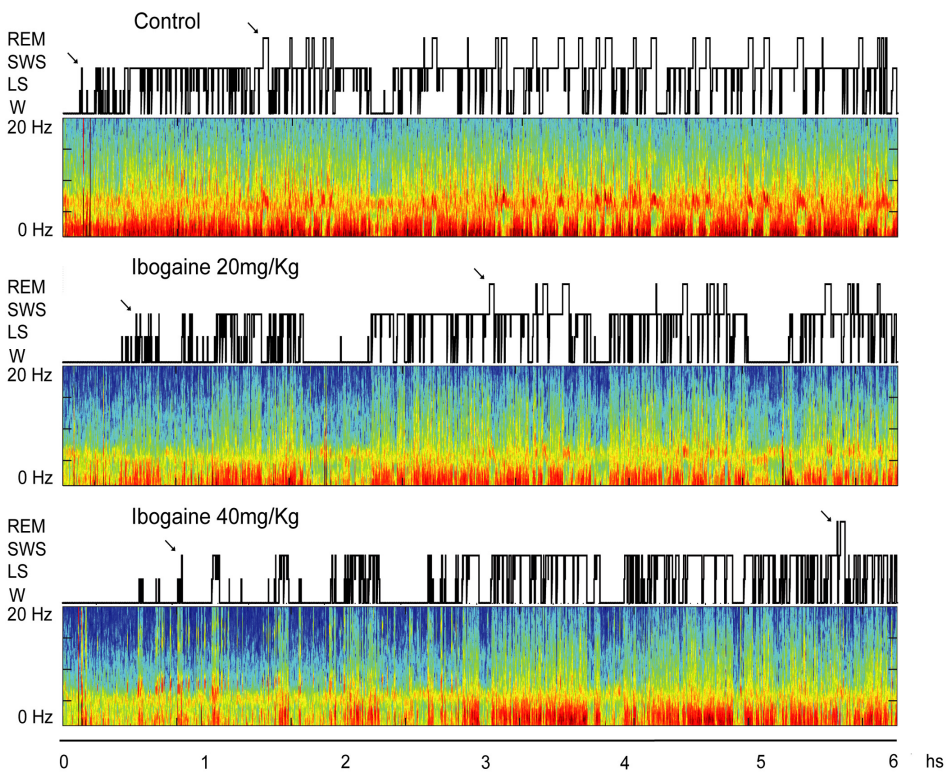


**FIGURE 1 |** Hypnograms and spectrograms (0.1–20 Hz) from the parietal cortical recordings of a representative animal are shown after saline, ibogaine 20 and 40 mg/kg. Arrows in the hypnogram indicate SWS and REM sleep latencies. During wakefulness (W) and REM sleep, theta activity (4–9 Hz) in the spectrograms can be readily observed. During SWS sleep, delta activity (0.5–4 Hz) is more prominent and there are intermittent episodes of sigma activity (9–15 Hz), which correspond to the presence of sleep spindles. Color calibration of the spectrogram is not exhibited (larger power is exhibited in red). Ibogaine increased W and reduced REM sleep time. LS, light sleep; REM, rapid eyes movements sleep; SWS, slow wave sleep.

During all experiments, the OF was cleaned with alcohol 30% before placing the following rat. All experiments were done between 9 AM and 3 PM.

## Data Analysis

### Sleep Recordings

All values are presented as mean ± SEM. The experimental design for the sleep analysis was a within-subject design, where statistical significance of the differences among groups (ibogaine 0, 20, and 40 mg/kg) was evaluated utilizing one-way repeated measures analysis of variance (ANOVA) and Bonferroni as a *post hoc* test (Monti et al., 2015). When sphericity criteria were not accomplished (tested by Mauchly's test), the Greenhouse–Geisser correction was applied. Statistical significance was set at $p < 0.05$.

### Motor Behavior

Depending on the comparison performed, data from motor activity were analyzed by two-way (treatment, time, and interaction between factors) ANOVA for repeated measures followed by Newman–Keuls multiple comparison *post hoc* test; or by one-way (treatment) ANOVA for independent measures followed by Newman–Keuls multiple comparison test. In all cases, statistical significance was set at $p < 0.05$.

# RESULTS

## Ibogaine's Effect on Wakefulness and Sleep

**Figure 1** shows a typical hypnogram and spectrogram of a representative animal following saline, $I_{20}$, and $I_{40}$ administration. Compared to control, $I_{20}$ [$F_{(1.1,8.3)} = 10.7$, $p < 0.01$] and $I_{40}$ [$F_{(1.1,8.3)} = 10.7$, $p < 0.05$] increased the time spent in W (**Figure 1** and **Table 1**). This effect was accompanied by a decrease in SWS time, $I_{20}$ [$F_{(2,14)} = 14.7$, $p < 0.01$], $I_{40}$ [$F_{(2,14)} = 14.7$, $p = 0.01$]. In addition, the total amount of REM sleep was diminished in animals treated with $I_{20}$ [$F_{(2,14)} = 19.3$, $p < 0.01$] and $I_{40}$ [$F_{(2,14)} = 19.3$, $p < 0.005$]. No differences on the total amount of LS were observed.

When considering the duration and number of episodes (**Table 1**), we found that compared to control, there was a significant increase in the duration of the individual W episodes after $I_{20}$ [$F_{(1.1,7.9)} = 6.4$, $p < 0.05$], and a decrease in the duration of SWS episodes for $I_{40}$ [$F_{(2,14)} = 9.5$, $p < 0.005$]. Regarding REM sleep, both doses of ibogaine reduced the total number of episodes [$F_{(1.2,8.5)} = 10.5$; $p < 0.05$ for $I_{20}$ and $I_{40}$] without affecting the episodes' duration. Finally, REM sleep latency increased following $I_{40}$ administration [$F_{(2,14)} = 9.6$, $p < 0.05$] (**Table 1**), while the latency to LS and SWS was not affected.

Ibogaine effects were also analyzed in 2-h blocks (**Figure 2**). Compared to control, the time of W was significantly increased for both doses in the first 2 h of the recording [$F_{(2,14)} = 9.1$, $p < 0.05$ for $I_{20}$ and $I_{40}$]. This increment was accompanied by a decrease in SWS [$F_{(2,14)} = 10.2$, $p < 0.05$ for $I_{20}$, and $p < 0.01$ for $I_{40}$] and REM sleep [$F_{(2,14)} = 17.8$, $p < 0.05$ for $I_{20}$, and $p = 0.001$ for $I_{40}$] without any appreciable change in LS. Within the second 2 h, a decrease in the REM sleep was observed following $I_{40}$ [$F_{(2,14)} = 8.7$, $p < 0.05$], while in the last 2 h, both $I_{20}$ and $I_{40}$ decreased REM sleep time [$F_{(1.1,7.8)} = 8.3$, $p < 0.005$ for $I_{20}$, and $p < 0.05$ for $I_{40}$].

## Ibogaine's Effect on Motor Behavior

In order to obtain further insights about the animal behavior during the ibogaine-induced waking state, a detailed study of motor behaviors was carried out (**Figures 3**, **4**). Compared to the control group, horizontal locomotion was slightly altered by both doses of ibogaine (**Figure 3A**). Two-way ANOVA revealed a significant effect of the treatment [$F_{(2,15)} = 8.7$, $p < 0.01$], time [$F_{(23,345)} = 12.2$, $p < 0.001$], and treatment × time interaction [$F_{(46,345)} = 1.43$, $p < 0.05$]. Newman–Keuls test showed that compared to control and $I_{20}$, $I_{40}$ elicited a significant decrease ($p < 0.001$) in the distance that the animals moved during the first 5 min; the animals injected with $I_{20}$ or saline exhibited a very similar level of locomotor activity (**Figure 3A**). When the total locomotor activity was analyzed (**Figure 3A** inset), one-way ANOVA revealed a significant difference between groups [$F_{(2,15)} = 8.7$, $p < 0.01$]. *Post hoc* analysis showed that $I_{20}$ elicited a significant increment in the locomotor activity compared to control ($p < 0.01$) and $I_{40}$ ($p < 0.05$) groups. The abovementioned decrease in novelty-induced locomotor activity observed in the $I_{40}$-treated animals at the beginning of the recording was not evidenced when the total activity period was considered (**Figure 3A** inset).

Rearing is a component of the natural exploratory behavior directly related to the environment novelty (Fink and Smith, 1980; Geyer et al., 1986; Bardo et al., 1990). In **Figure 3B**, we can observe that naive rats were more active mainly in the first period of the recording session; in fact, the control group seems to be rapidly habituated to the OF apparatus and becoming virtually inactive at the end of the 60-min recording time. Statistical two-way ANOVA analysis revealed a significant effect of the treatment [$F_{(2,15)} = 4.0$, $p < 0.05$], time [$F_{(4,60)} = 14.6$, $p < 0.001$], and the treatment × time interaction [$F_{(8,60)} = 2.4$, $p < 0.05$]. Newman–Keuls test showed that animal injected with $I_{40}$ ($p < 0.001$), but not $I_{20}$, significantly reduced the ability to induce rearing behavior during the first 5 min, suggesting an alteration in the environment habituation response (**Figure 3B**). When the total rearing activity was considered (**Figure 3B** inset), one-way ANOVA did not reveal a significant difference between groups [$F_{(2,15)} = 3.4$, $p = 0.06$], although this behavior was still not correctly restored.

**Figures 4A,B** show the effect of the ibogaine on the induction of serotonin syndrome-like behaviors and HSR, respectively. In order to simplify, only the first 5 min session is shown. One-way ANOVA analysis revealed significant differences between experimental groups for tremor [$F_{(2,15)} = 35.9$, $p < 0.0001$] and flat body posture [$F_{(2,15)} = 9.3$, $p < 0.01$] but not for forepaw treading [$F_{(2,15)} = 1.2$, $p = 0.3$)] or piloerection [$F_{(2,15)} = 1.2$, $p = 0.1$]. Straub tail and hind limb abduction were not seen (data not shown). *Post hoc* analysis showed that tremor and flat body posture were significantly present immediately after $I_{40}$ injection ($p < 0.001$ and $p < 0.01$, respectively, **Figure 4A**), while these behaviors were completely absent at the end of the 60 min session (data not shown). Animal treated with $I_{20}$ did not significantly elicit these behavioral signs. Since only these two behaviors were significantly elicited by $I_{40}$, an overall serotonin syndrome (Haberzettl et al., 2013) cannot be referred as induced by ibogaine in these conditions. Additionally, one-way ANOVA for the HSR did not reveal significant difference [$F_{(2,15)} = 1.1$, $p = 0.36$] neither for $I_{20}$ nor for $I_{40}$ during the total 120 min session (**Figure 4B**).

**TABLE 1 |** Effects of intraperitoneal injections of ibogaine on sleep and waking parameters during total recording time.

| | Control | Ibogaine 20 mg/kg | Ibogaine 40 mg/kg |
|---|---|---|---|
| **Wakefulness** | | | |
| Total duration (min) | 95.1 ± 7.8 | 135.5 ± 9.8* | 182.6 ± 26.6* |
| Number of episodes | 118.0 ± 8.9 | 130.8 ± 8.1 | 127.1 ± 10.4 |
| Episodes duration (min) | 0.8 ± 0.0 | 1.0 ± 0.1* | 1.5 ± 0.2 |
| **Light sleep (LS)** | | | |
| Total duration (min) | 32.6 ± 2.6 | 39.4 ± 3.0 | 37.6 ± 4.3 |
| Number of episodes | 152.6 ± 3.4 | 173.7 ± 4.4 | 163.2 ± 5.4 |
| Episodes duration (min) | 0.21 ± 0.0 | 0.2 ± 0.0 | 0.22 ± 0.0 |
| **Slow wave sleep (SWS)** | | | |
| Total duration (min) | 197.8 ± 8.0 | 162.3 ± 7.3* | 127.4 ± 19.6* |
| Number of episodes | 141.5 ± 7.4 | 152.5 ± 13.7 | 124.8 ± 7.8 |
| Episodes duration (min) | 1.4 ± 0.9 | 1.1 ± 0.8 | 1.0 ± 0.8* |
| Latency | 9.1 ± 1.7 | 21.8 ± 3.6 | 53.2 ± 14.9 |
| **REM sleep** | | | |
| Total duration (min) | 33.6 ± 2.5 | 22.0 ± 2.8* | 11.5 ± 3.7* |
| Number of episodes | 25.1 ± 2.3 | 19.6 ± 2.6* | 11.8 ± 4.7* |
| Episodes duration (min) | 1.3 ± 0.0 | 1.1 ± 0.1 | 0.8 ± 0.2 |
| Latency (min) | 72.5 ± 2.7 | 137.1 ± 24.8 | 229.8 ± 43.4* |

*Data are presented as mean ± standard error of eight rats. *Symbols denote significant difference compared with control values using ANOVA repeated measures followed by Bonferroni test ($p < 0.05$).*

# DISCUSSION

In the present study, we showed that administration of 20 and 40 mg/kg of ibogaine produced a robust effect on sleep and W, promoting a waking state that is accompanied by a robust and long-lasting REM sleep suppressive effect. The higher dose ($I_{40}$) showed, in addition, a time-dependent disability to explore a novel environment, as well as disabling behaviors like tremor and flat body posture. It is well-established that ibogaine is rapidly metabolized to its long-lived metabolite noribogaine, so both substances should be taken into account to explain

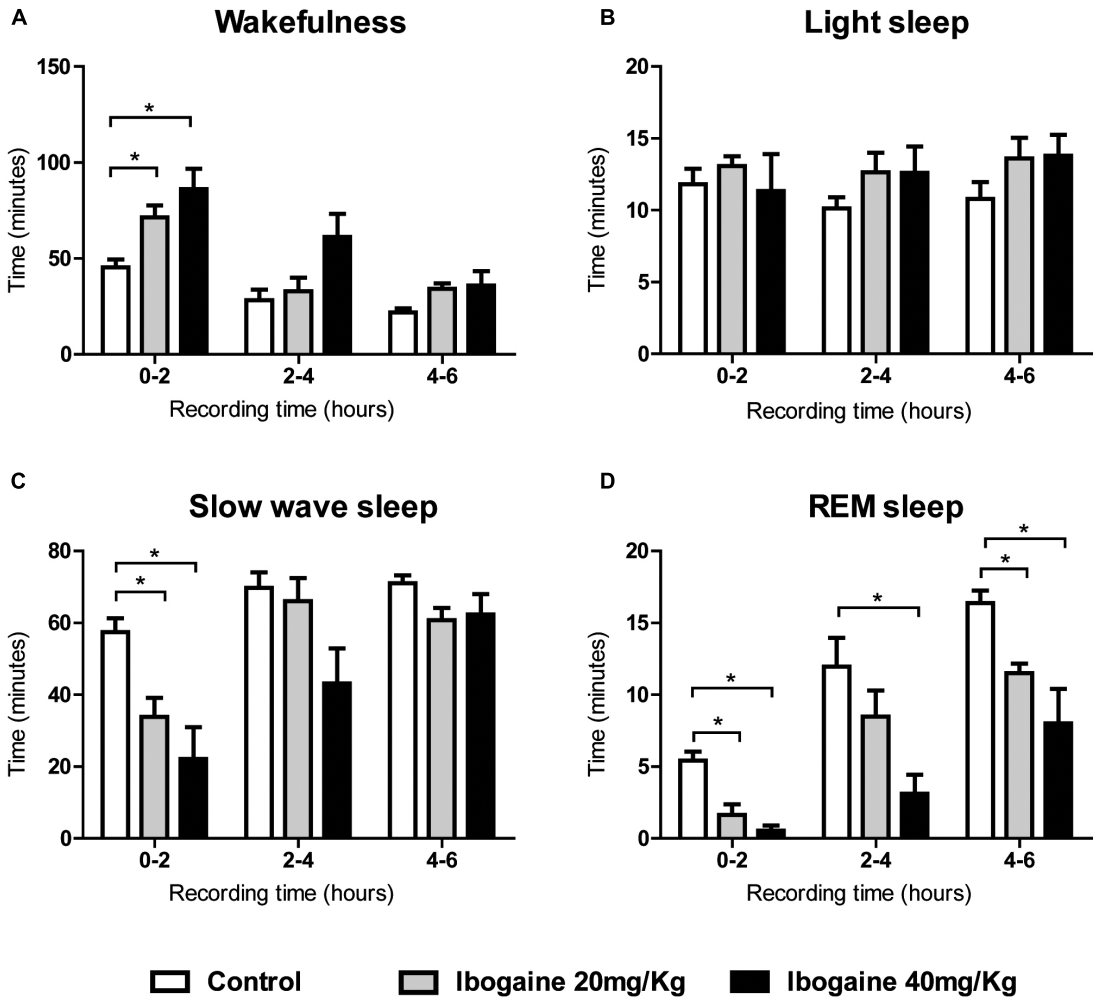


**FIGURE 2 |** Effects of ibogaine administration on sleep and W. Graphic chart shows the mean ± SEM time spent in **(A)** W, **(B)** light sleep, **(C)** slow wave sleep, and **(D)** REM sleep after administration of saline and ibogaine (20 and 40 mg/kg), analyzed in 2-h blocks. Group mean differences were determined by one-way ANOVA repeated measures and Bonferroni as *post hoc* test; significant differences ($p < 0.05$) between groups are indicated by asterisks. Eight animals were employed in this analysis.

the findings of this study. According to previous reports in rats using i.p. administration (Baumann et al., 2001a), ibogaine concentration in blood rapidly decreases in the first hour while noribogaine concentration is maximum at 2.4 h and lasts up to 24 h. Since it is known that ibogaine induces tremors while noribogaine does not (Baumann et al., 2001a), the fact that we only found tremors during the first hour of recordings for $I_{40}$ seems to be in accordance with this pharmacokinetic profile.

Ibogaine administration promoted W; this effect was accompanied by a decrease in the total amount of SWS and REM sleep. While the effects on W and SWS were observed only in first 2 h, the effects on REM sleep lasted through the entire recording. These results may resemble observational studies in humans where ibogaine administration in multiple doses produced difficulties in sleep onset and maintenance immediately after each intake (Wilkins et al., 2017). Ibogaine's W-promoting effect, in addition, is in accordance with a previous report in cats (Schneider and Sigg, 1957), suggesting that ibogaine induces W in rats, cats, and probably in humans.

Interestingly, a similar impact upon sleep architecture has been reported for traditional psychedelics ($5HT_{2A}$ agonists), such as LSD (also a $5HT_{2C}$ receptor agonist) and 2,5-dimethoxy-4-iodoamphetamine (DOI, also a $5HT_{2C}$ agonist) (Depoortere and Loew, 1971; Monti and Jantos, 2006). Chronic LSD treatment in rats promotes an increase in W and a reduction in SWS and REM sleep. Similar to ibogaine, the W-promoting effect was more prominent during the first hour, while it disappeared after 4 h. The authors also found qualitative changes in REM sleep, reporting an increase in phasic episodes as well as an increase in rapid eye movements. Subcutaneous administration of DOI also increases W and decrease SWS and REM sleep. Together these results suggest that ibogaine and traditional psychedelics induce similar effects on sleep architecture. Regarding selective antagonists of $5HT_{2A}$ and $5HT_{2C}$ receptors, it was found that their administration promotes SWS; while surprisingly decreases

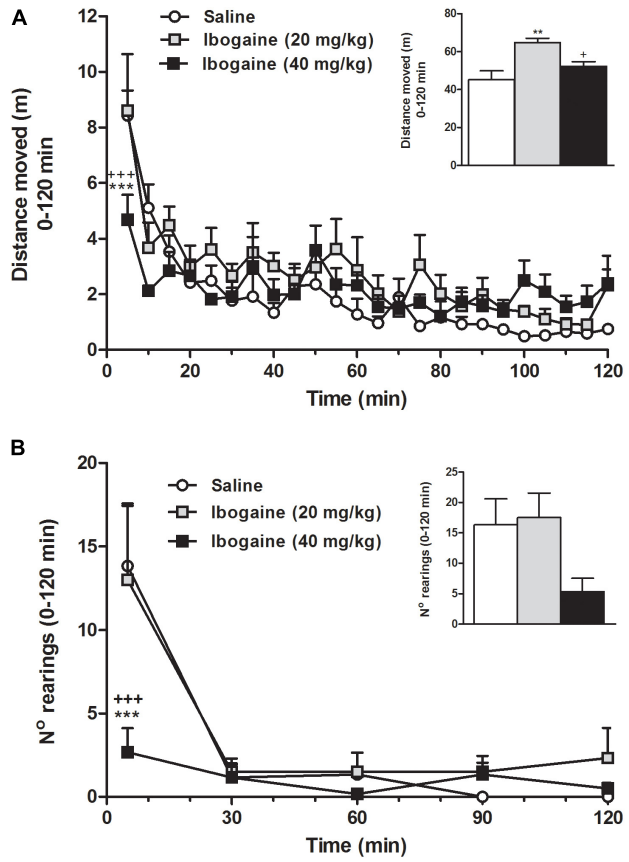


**FIGURE 3 |** Effect of ibogaine administration (20 and 40 mg/kg) on locomotor activity **(A)** and exploratory activity (**B**; number of rearings) recorded in the OF test during 120 min after ibogaine administration. The inset graphs represent the total locomotor activity and the total number of rearings (0–120 min). Data are expressed as mean ± SEM. The data were analyzed by the two-way ANOVA of repeated measured followed by Newman–Keuls test, and one-way ANOVA of independent measures followed by Newman–Keuls test (insets). *, respective to saline group; +, respective to ibogaine. ***, $^{+++}p < 0.001$; **$p < 0.01$; $^{+}p < 0.05$. $N = 6$ per group.

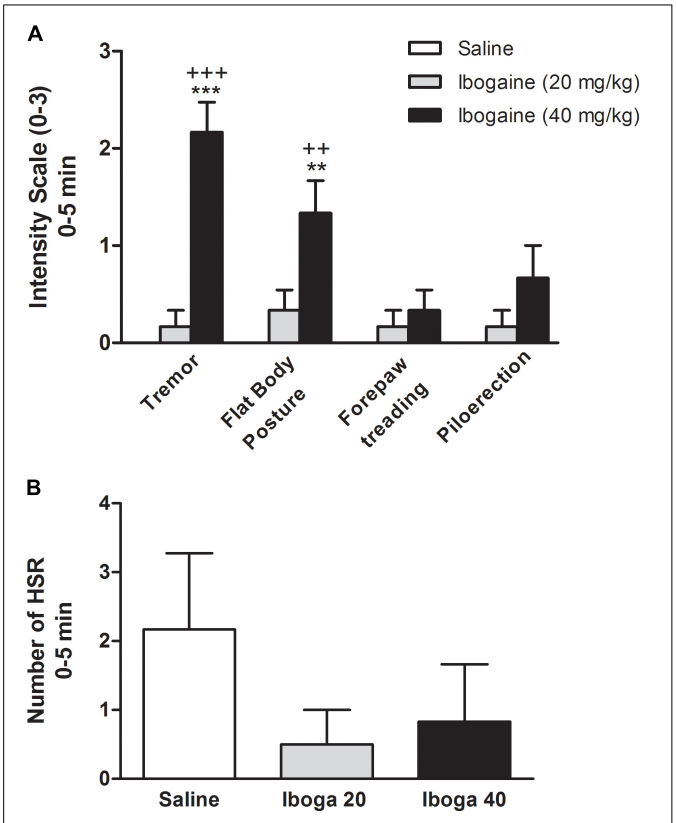


**FIGURE 4 |** Effects of ibogaine on behavior. Specific behaviors such as tremor, flat body posture forepaw treading, piloerection **(A)**, and head shake response (HSR) **(B)** were shown during the first 5 min after ibogaine administration. In **A**, behaviors were scored using the graded scale: 0, absent; 1, equivocal; 2, present; and 3, intense while in **B**, the number of HSR was scored. Data are expressed as mean ± SEM and analyzed by one-way ANOVA of independent measures followed by Newman–Keuls test. *, respective to saline group and +, respective to ibogaine. ***, $^{+++}p < 0.001$; **, $^{++}p < 0.01$. $N = 6$ per group.

REM sleep time (Monti and Jantos, 2006; Monti et al., 2018). These unexpected results have not been explained yet.

Since dreams are the cognitive counterpart of REM sleep (although dreams under NREM sleep may also occur), the long-lasting REM sleep suppression induced by ibogaine administration seems at first sight to be against its previously mentioned oneirogenic properties. However, this may not be the case, since a quantitative analysis of the EEG during W could provide evidence of an altered W pattern. For example, ibogaine-induced W may present a decrease in gamma band coherence, which is a well-known electrophysiological signature of REM sleep (Castro et al., 2013; Cavelli et al., 2015, 2017a). In other words, this pharmacologically-induced W state could have subtle electrophysiological traits of REM sleep that could explain the oneirogenic cognitive effect of the drug. With the aim of answering this question, a quantitative analysis of the EEG (power, coherence, co-modulation, entropy) is under process and will be reported in due course. In addition, this type of analysis would be helpful to compare the quality of W produced by ibogaine to traditional psychedelics.

Which are the underlying mechanisms of the W-promoting and REM sleep suppressive effects? Experiments in synaptosomes have shown that ibogaine inhibits serotonin re-uptake, which increases the synaptic levels of this neurotransmitter (Wells et al., 1999). In addition, Wei et al. (1998) showed that ibogaine elicited a large increase in serotonin levels (up to 25-fold in the Nucleus Accumbens, NAC and 10-fold in the striatum, STR) while noribogaine produced a moderate increase (up to eightfold in NAC and fivefold in STR) (Wei et al., 1998). In contrast, Baumann et al. (2001b) showed that noribogaine was more potent in increasing serotonin levels at the NAC than ibogaine, which correlates with the ability of both compounds to inhibit SERT ($IC_{50}$ of 3.85 and 0.18 μM for ibogaine and noribogaine, respectively). These authors suggested that ibogaine and noribogaine are serotonin-reuptake inhibitors with a mechanism of action similar to fluoxetine. Serotonin increases W and suppress the generation of REM sleep (Oniani and Akhvlediani, 1988; Monti and Jantos, 2005). Hence, the ability

of ibogaine and noribogaine to increase synaptic serotonin concentration could account for the increment in W time, as well as the long-lasting REM suppressive effect. The fact that most antidepressant drugs share this REM sleep suppressing effect (Palagini et al., 2012), insinuate that ibogaine might also have antidepressant properties as suggested by human reports (Mash et al., 2000).

Schneider and Sigg (1957) also proposed that the activation of the cholinergic pathways should be involved in the effects produced by ibogaine. In this regard, mesopontine and basal forebrain cholinergic neurons are involved in the generation and maintenance of W (Torterolo et al., 2016). Hence, it is likely that by modulation of these neurochemical systems ibogaine can promote W and suppress sleep. Nevertheless, because of its complex pharmacology, the interactions between other neurotransmitters, as well as the still unknown effects of ibogaine on REM sleep promoting neurons such as the melanin-concentrating hormone (MCH) containing neurons, should be taken into account when interpreting these results (Torterolo et al., 2011; Monti et al., 2013).

Another possibility is that the increase in W could be caused by some unspecific effect, such as irritation or pain. In this regard, we did not observe any behavior suggesting this kind of effect. In fact, it is interesting to consider that there is evidence of ibogaine as an anti-nociceptive agent (Olney, 1995, 1997). Moreover, both ibogaine and noribogaine enhance morphine anti-nociception (Bagal et al., 1996), and to our knowledge, there are no observational studies which reported pain or inflammation after ibogaine administration in humans.

When considering the results seen in each 2-h block, we hypothesized that the different effects seen along the entire recording could be attributed not just to ibogaine itself, but also to its principal metabolite, noribogaine. As mentioned before, according to previous reports using i.p. administration in rats, ibogaine concentration in blood rapidly decreases in the first hour (with a T-max of approximately 0.1 h), while noribogaine is detectable in blood up to 24 h after ibogaine administration (with a T-max of approximately 2.4 h) (Baumann et al., 2001b). Hence, the increased W found in the first 2-h block could be correlated to the peak concentration of ibogaine in addition to increasing amounts of noribogaine, while the extended REM suppression seen through the entire recording could be attributed to the long-lasting noribogaine. Further experiments are needed to confirm this hypothesis.

Regarding motor behavior, a higher total locomotor activity was found after $I_{20}$ administration suggesting a more vigilant animal response. This stimulant effect is in accordance with previous findings that showed that 1 and 10 mg/kg i.v. doses promoted a dose-dependent increase in locomotor activity in rats (Baumann et al., 2001b). In contrast, $I_{40}$ administration did not show a substantial increase in locomotor activity, producing serotonin syndrome-like behaviors such as tremor and flat body posture mainly during the first part of the recording session. It is likely that the appearance of these behaviors would explain, at least in part, the abnormal environment animal habituation response to the OF (**Figure 3A**), and reduced the ability to induce rearing behavior that was found after the administration of this dose (**Figure 3B**). Taken together, these results clearly indicate that $I_{40}$ induces a kind of W that is different than the one produced by the lower dose. These results may resemble subjective experience of natives from Congo and Gabon who used low doses of *T. iboga* root bark as a powerful stimulant to combat fatigue and tiredness, while larger doses were chosen to produce visions in ritual settings (Schneider and Sigg, 1957; Pope, 1969).

The ibogaine induced tremor and flat body posture (**Figure 4A**), suggest a putative interaction with serotonin transmission. However, Baumann et al. (2001b) have postulated that a serotonergic mechanism may not be involved in the locomotor effects of ibogaine, since according to their results noribogaine (which is not tremorgenic in rats) is more potent in increasing serotonin levels than ibogaine. In this manner, they speculate that sigma or NMDA receptors might also explain these behaviors (since noribogaine has less affinity for this sites) (Baumann et al., 2001b). Regarding the induction of HSR, no changes were found for both ibogaine treatments (**Figure 4B**). As mentioned before, this behavior is exacerbated by the systemic administration of $5HT_{2A}$ receptor agonists (like classical hallucinogens). This constitutes a putative behavioral difference for animals treated with hallucinogens (LSD, DOI, etc.) versus ibogaine, which is considered a non-traditional psychedelic. Pharmacological data also favor this difference, while hallucinogens interact with the 5-$HT_{2A}$ receptor in the nanomolar range, ibogaine affinity for this receptor is in the micromolar range ($K_i$ 4.8–92.5 μM depending the study) (Repke et al., 1994; Sweetnam et al., 1995; Helsley et al., 1998; Glick et al., 1999) or negligible (Deecher et al., 1992; Staley et al., 1996). At last, this difference is also supported by the differences between the subjective experiences in humans where ibogaine does not produce the typical interferences in thinking, identity distortions, and space–time alteration produced by the traditional psychedelics drugs (Naranjo, 1973). In summary, the sleep and motor effects induced by ibogaine, and its differences with classical hallucinogens, can only be explained by the interaction of ibogaine with several neurochemical systems.

## CONCLUSION AND FUTURE PERSPECTIVES

In this study, we observed that intraperitoneal administration of ibogaine in rats produced an increase in W, a decrease in SWS along with a robust suppression of REM sleep. Although these effects on sleep and W were observed for both doses of ibogaine (20 and 40 mg/kg), locomotor studies indicated differences in the behavioral outcomes for both treatments. While the $I_{20}$ dose had a stimulant profile, the $I_{40}$ dose generated an abnormal environment habituation where significant tremor and flat body posture were detected. Hence, given that ibogaine is considered an oneirogenic psychedelic, the next step would be to analyze the specific electroencephalographic characteristics of the pharmacologically induced W, such as the power spectrum and spectral coherence between different cortical areas. This kind

of analysis could provide further insights of the cognitive activity induced by this drug.

## ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the National Animal Care Law (No. 18611) and with the "Guide to the care and use of laboratory animals" (8th edition, National Academy Press, Washington DC, 2010). Furthermore, the Institutional Animal Care Committee (Facultad de Medicina – Universidad de la República; Instituto de Investigaciones Biológicas Clemente Estable) approved the experimental protocols. Adequate measures were taken to minimize pain, discomfort, or stress of the animals, and all efforts were made to use the minimal number of animals necessary to obtain reliable scientific data.

## AUTHOR CONTRIBUTIONS

IC, GS, PT, and CS provided the financial support. IC, PT, and CS performed the experimental design. JG, JP, PR, MC, LB, AM, and MP performed the experimental procedures. JG, MC, JP, IC, PT, CS, and GS were involved in the analysis of the data. JG, MC, JP, GS, IC, PT, and CS were involved in the discussion and interpretation of the data. JG, IC, PT, and CS wrote the manuscript. All the authors participated in the critical revision of the manuscript, added important intellectual content, and approved the definitive version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2018.00374/full#supplementary-material

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