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Pharmacology Biochemistry and Behavior, Vol. 53, No. 2, pp. 257-264, 1996

0091-3057/96 $15.00 + .00

0091-3057(95)00209-X

Role of 5-HT_{1b} Receptor in the Pressure-Induced Behavioral and Neurochemical Disorders in Rats

BADREDDINE KRIEM, JACQUES H. ABRAINI AND JEAN-CLAUDE ROSTAIN[1]

Laboratoire de Physiopathologie Respiratoire Intégrée et Cellulaire, Equipe de Neurobiologie en Conditions Extrêmes, CNRS-URA 1630, Institut Jean Roche, Faculté de Médecine Nord, 13916 Marseille Cedex 20, France

Received 10 February 1995; Revised 5 April 1995; Accepted 17 May 1995

KRIEM, B., J. H. ABRAINI AND J.-C. ROSTAIN. *Role of 5-HT_{1b} receptor in the pressure-induced behavioral and neurochemical disorders in rats.* PHARMACOL BIOCHEM BEHAV **53**(2) 257-264, 1996.—When human divers and experimental animals are exposed to increasing environmental pressure, they develop the high-pressure neurologic syndrome (HPNS) that has been recently demonstrated to include an increase in striatal dopamine (DA) release. This increase has been correlated with enhanced locomotor and motor activity (LMA). In the present study, we investigated the effect of the 5-HT_{1b} receptor antagonist (±)cyanopindolol, which has been shown to block at normal pressure the increase in striatal DA release induced by the administration of the 5-HT_{1b} receptor agonist CGS 12066B. Our data clearly showed that the administration of (±)cyanopindolol partially blocked both the pressure-induced increase in striatal DA release and the development of LMA. These results suggest the contribution of the 5-HT neurotransmission in the DA-related neurochemical and behavioral disorders that occur in rats exposed to high pressure.

Dopamine Serotonin 5-HT_{1b} receptors Striatum Pressure HPNS Locomotor activity (±)Cyanopindolol Voltammetry

HIGH pressure is known as a basic etiologic factor underlying CNS changes referred to as the high-pressure neurologic syndrome (HPNS) (11,12,18). This syndrome is observed when human divers or experimental animals are exposed to high pressure > 15-20 bar. The principal symptoms of this syndrome include electroencephalographic changes, sleep disturbances, muscle tremor, and myoclonia. Animals also developed locomotor and motor activity (LMA), and for pressures higher than humans have reached, convulsions and epileptic seizures. These symptoms have been described by several authors and reviewed elsewhere (10,20).

Several in vitro and in vivo neurochemical studies have demonstrated that high pressure induced an increase in dopamine (DA) release in both the striatum (4,17,26,31,34) and the nucleus accumbens (5). This elevation of DA release in both brain regions has been further shown to correlate with the development of LMA in rats exposed to high pressure (4,5). In addition, other studies have also demonstrated the crucial role of DA receptors in both the occurrence of LMA and the increase in DA release (2,7), and further suggested possible interactions (1,2) between pressure-induced changes in DA neurotransmission and other brain neurotransmitters (27,28, 36,41).

Thus, because recent studies have clearly demonstrated at normal pressure that the activation of the 5-HT_{1b} receptors may induce an increase in striatal DA release (8,9,19), we here report neurochemical and behavioral experiments in freely moving rats on the effects of the use of the 5-HT_{1b} receptor antagonist (±)cyanopindolol in the presence of the β-adrenergic receptor agonist (±)isoproterenol to antagonize binding of (±)cyanopindolol to the β-adrenergic receptors (14,21,22,30); these experiments reflect, for the first time to our knowledge, neurochemical interactions at high pressure between serotoninergic and dopaminergic systems. To better

[1] Requests for reprints should be addressed to J.-C. Rostain, Laboratoire de Physiopathologie Respiratoire Intégrée et Cellulaire, Equipe de Neurobiologie en Conditions Extrêmes, CNRS-URA 1630, Institut Jean Roche, Faculté de Médecine Nord, Bd. P. Dramard, 13916 Marseille Cedex 20, France.

determine these interactions, we investigated in the first part of the present study the effect of (±)cyanopindolol in the presence of (±)isoproterenol on the 5-HT_{1b} receptor agonist CGS 12066B-induced striatal DA increase. Electrochemical and behavioral measurements were performed using differential pulse voltammetry and DA-selective electrodes (13,15,16) and a piezoelectrical sensor device (38), respectively.

METHODS

Animals and Surgery

We used male Sprague-Dawley rats (n = 43) (Iffa-Credo, L'Arbresle, France) weighing 300-350 g at the time of surgery. Rats were housed at 21 ± 0.5°C in individual altuglass home cages under a 12 L : 12 D cycle (with lights on from 0700-1900 h) with free access to food and water.

Multifibre working carbon electrodes (see below) and stainless-steel cannulae [for the intracerebroventricular (ICV) administration of drugs] were stereotaxically implanted, according to the atlas of Konig and Klippel (25), in the dorsal caudate-putamen (A: 8.62, L: 2.0, H: 1.4), and the right lateral ventricle (A: 5.91, L: 1.4, H: 2.0), respectively, under general anesthesia [pentobarbital sodium 30 mg/kg, intraperitoneally (IP) and ketamine 100 mg/kg, intramuscularly (IM)]. The reference and auxilliary electrodes (stainless-steel screws) were fixed to the bone. The electrodes were attached to a miniconnector and the whole assembly of electrodes, cannulae, and connector was held in place with dental cement (resin cement; Ivoclar, Zurich, Switzerland).

After surgery, the animals were allowed to recover for 1 week before being submitted to the pharmacologic and pressure investigations.

At the end of the experiments, histologic controls were performed in some animals; the brain was removed and sliced, and the location of both the working carbon electrode and the cannulae were histologically checked, referring to the atlas of Konig and Klippel (25).

Electrodes and Electrochemical Measurements

Electrochemical measurements were made in vivo as first developed by Kissinger et al. (24) in the rat brain, using differential pulse voltammetry according to the method developed by Forni and Nieoullon (16). Voltammetric measurements were performed on unrestrained awake animals using a PRG5 polarograph (Taccussel, Villeurbanne, France), and a classical three-electrode potentiostatic system with reference, auxiliary, and working electrodes.

Multifibre carbon working electrodes were built as described previously (15), from a rigid rod of 10,000 carbon fibres (ref. AGT 4F 10,000; Carbone Lorraine, France) sharpened at one extremity to reduce the external diameter of the electrode from 1 mm to 50 μm at the tip. The entire electrode was encased in an insulating resin and the tip was exposed using an abrasive disc to shape the active surface of the electrode. Before use, the working carbon electrodes were electrochemically pretreated by applying a triangular wave potential of 0-3 V, 70 Hz, 20 s; 0-2 V, 70 Hz, 20 s; and 0-1 V, 70 Hz, 15 s, to increase their sensitivity to DA (13,15,16).

During voltammetric in vivo recordings, the animals were connected to the polarograph through a flexible cable and a swivel connector. The polarograph was set to the following parameters: scan rate 10 mV/s or 20 mV/s; voltage range 0-1000 mV; pulse modulation amplitude 50 mV; pulse modulation duration 48 ms; pulse period 0.2 s. Electrochemical signals were amplified (× 10) and recorded every 3 min; and DA release was quantified automatically by measuring the height of the DA oxidation peak, using a computerized device.

Electrode Calibration

Before being implanted, the working carbon electrode was calibrated in vitro in various solutions of DA, dihydroxyphenylacetic acid (DOPAC), ascorbic acid (AA), uric acid (UA), and homovanillique acid (HVA) of 10^{-8} M to 10^{-3} M to control their responsivity and their selectivity for DA as compared with the other compounds. As previously described (2,3, 13,16), the oxidation peaks of DA and DOPAC both occurred at 160 mV, whereas those of AA, UA, and HVA occurred at 90, 300, and 450 mV, respectively. The height of the voltammograms recorded in DA solutions of 10^{-8} M to 10^{-4} M consisted of electrochemical signals ranging from 3-40 nA, whereas no voltammograms were recorded in DOPAC, AA, UA, and HVA solutions $< 10^{-3}$ M.

During in vivo recordings in awake animals, voltammograms were amplified (× 10). Electrochemical responses with oxidation peaks similar to those recorded in DA solutions (peak range 150-180 mV) were obtained ranging from 1.5-4 nA; the corresponding extracellular striatal DA concentration ranged from 5×10^{-9} M to 5×10^{-8} M (3). In addition, in some animals, preliminary pharmacologic experiments were performed to further assess the in vivo selectivity of the pretreated multifibre carbone electrode for DA compared with DOPAC. During these experiments, the following drugs were delivered ICV, at a rate of 2 μl/min, in a volume of 10 μl phosphate-buffered saline (PBS) using a microsyringe : α-methyl-*p*-tyrosine (α-MPT) 10^{-7} mol (50 μg/kg); pargyline 2×10^{-7} mol (75 μg/kg) (Research Biomedicals, Natick, MA). Results showed that ICV administration of α-MPT, an inhibitor of DA synthesis, significantly decreased the amplitude of the DA electrochemical response, whereas ICV administration of pargyline, a monoamine oxydase inhibitor that blocks DOPAC formation, significantly increased striatal DA release (Fig. 1).

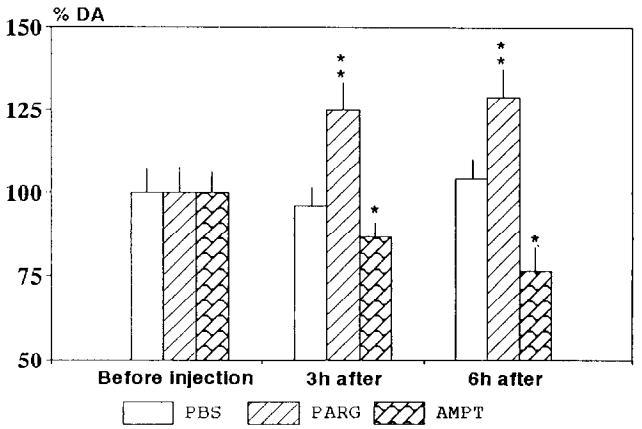

FIG. 1. Preliminary pharmacologic experiment to assess further the in vivo selectivity of the pretreated multifibre carbone electrode for DA compared with DOPAC. Effect of ICV administration of α-methyl-*p*-tyrosine (AMPT), an inhibitor of DA synthesis, at a dose of 10^{-7} mol (50 μg/kg), and pargyline, at a dose of 2×10^{-7} mol (75 μg/kg), an MAOI that blocks DOPAC formation. Median and the 25th to 75th percentiles were n = 4 for AMPT, and n = 5 for pargyline. U-test: $*p < 0.005$, $**p < 0.002$ vs. vehicle-treated rats.

All of these data confirmed, as previously reported in details by several authors, that the pretreated multifibre carbon electrode has a high responsivity and sensitivity for DA compared with other endogenous compounds including DOPAC.

Behavioral Analysis

Behavioral analysis was performed as described previously by Tomei et al. (38). Principles of analysis can be summarized as follows: behavioral symptoms of HPNS were obtained from piezoelectrical sensors that were fixed under the floor of each altuglass cylinder; signals were quantitatively analyzed on a PC-AT-compatible computer, and decomposed on line in LMA and myoclonia. Myoclonia were detected as signals of unusual high amplitude (with a threshold of detection adjustable for each rat); and LMA as the whole signal minus myoclonia. LMA and myoclonia are expressed in arbitrary units (U).

Exposure to Pressure

During pressure experiments, freely moving animals were placed in separate altuglass cylinders in a 50-l pressure chamber (maximum pressure 200 bar) in which the 12 L : 12 D regime was maintained. Then, 30 min after PBS or drug administration, rats were compressed with helium to a relative pressure of 80 bar at a rate of 1 bar/min. Oxygen was maintained at a constant partial pressure of 0.4 bar, which is the partial pressure generally used in human dives. The CO_2 was $< 0.003\%$. Humidity was controlled and temperature was progressively increased from 25 to 33°C to prevent hypothermia and maintain the comfort of the animals, because of the important specific heat of helium as compared with air. The stay at the maximal pressure lasted 2 h, and the decompression 24 h. Animals were decompressed at a rate of 0.06 bar/min from 80 to 12 bar and 0.04 bar/min from 12 bar to normal pressure. During decompression, partial pressure of oxygen was 0.5 bar. All animals survived the pressure experiments.

Drug Treatments

Drugs were delivered ICV, at a rate of injection of 2 μl/min, in a volume of 10 μl PBS, using a microsyringe. Control animals received vehicle alone. The following drugs were used: CGS 12066B 2×10^{-8} mol (30 μg/kg), (±)isoproterenol 2 ×

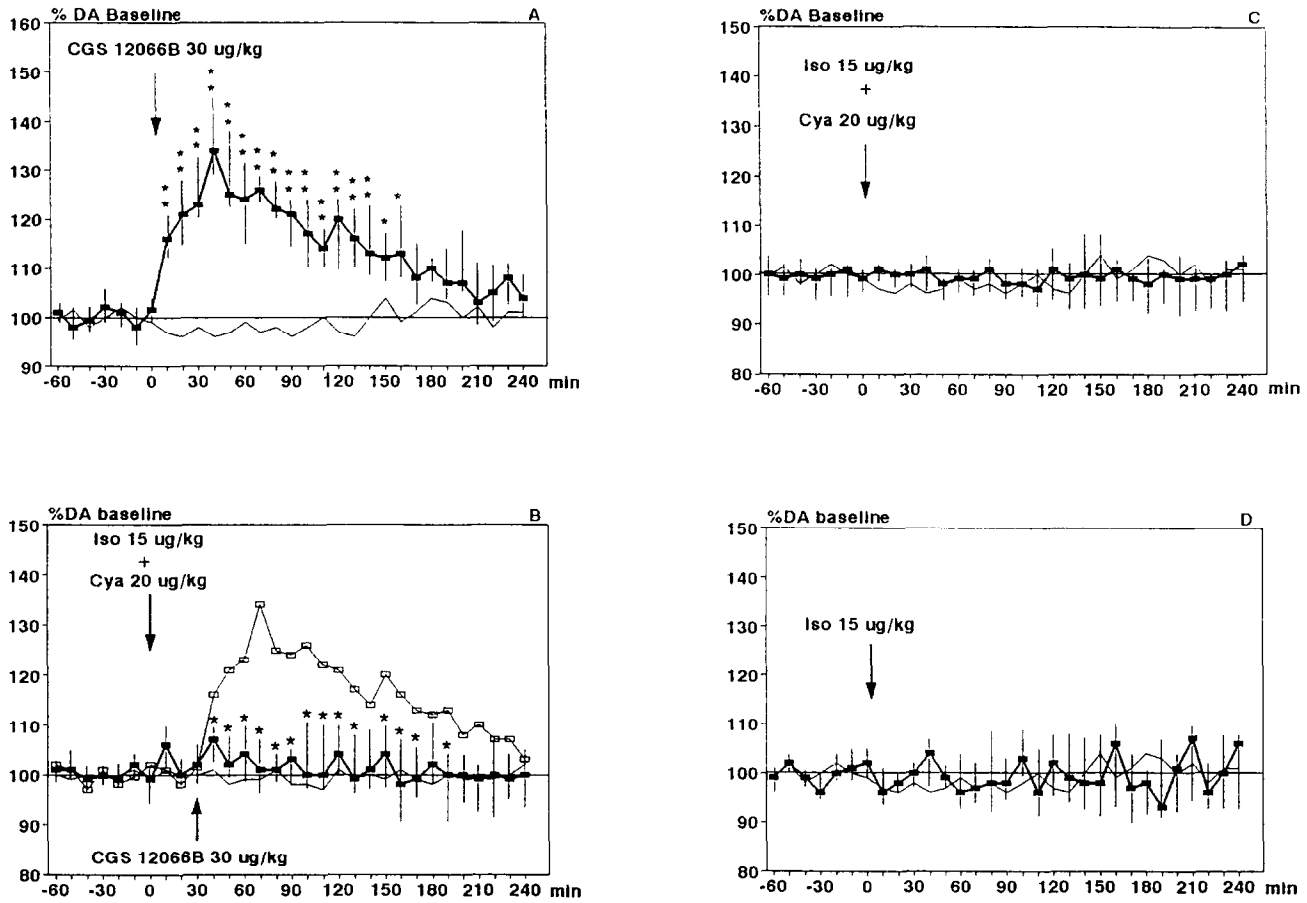

FIG. 2. Dopamine release recorded from the caudate-putamen of freely moving rats after administration of (A) 30 μg/kg 5-HT_{1b} receptor agonist CGS 12066B, *U*-test: $*p < 0.05$, $**p < 0.005$ vs. vehicle-treated rats ($n = 6$, —); (B) 20 μg/kg (±)cyanopindolol, in the presence of 15 μg/kg (±)isoproterenol, before CGS 12066B administration, *U*-test: $*p < 0.05$ vs. CGS 12066B experiments (-□-); (C) and (D) 20 μg/kg (±)cyanopindolol in the presence of 15 μg/kg (±)isoproterenol, and 15 μg/kg (±)isoproterenol, respectively: no significant effect was found upon striatal DA release. DA release is expressed as a percentage from a 70-min period of control before drug administration. For each drug, median values and the 25th to 75th percentiles were obtained from $n = 4$ rats. Arrows indicate time of drug administration.

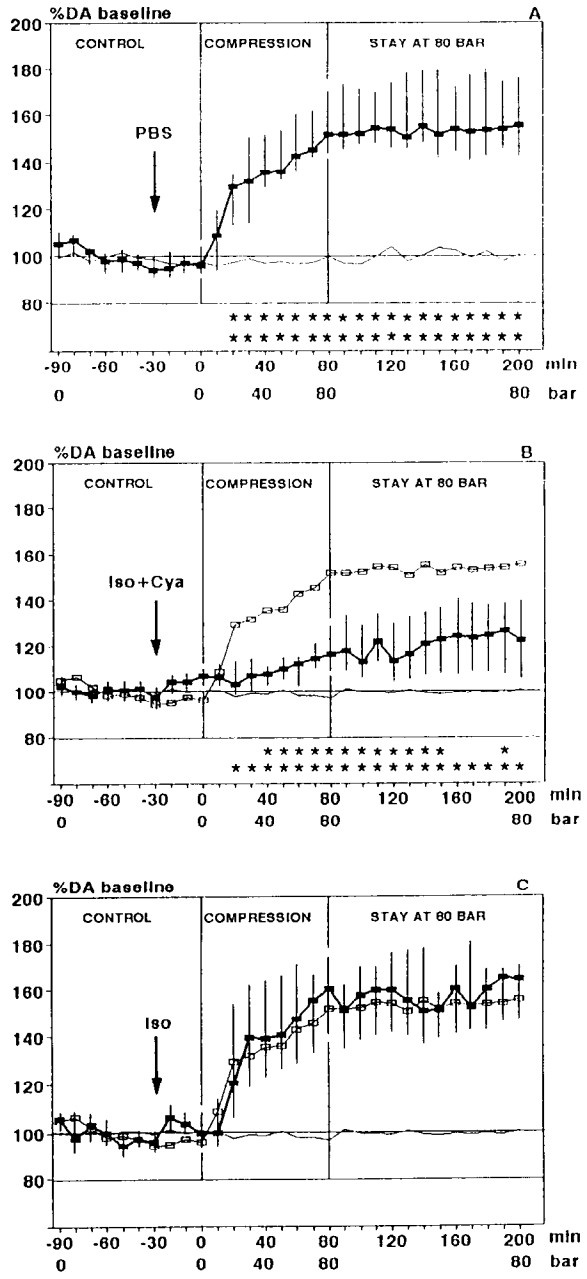

FIG. 3. Dopamine release recorded from the dorsal caudate-putamen of freely moving rats exposed to 80 bar of high pressure. Y-axis: DA increase expressed as a percentage from control values (70 min) using median values ± 25th to 75th percentiles. X-axis: pressure expressed in bar (1 bar = 10^{+5} Pa) and time expressed in minutes. (A) Vehicle-treated rats exposed to high pressure (n = 4), U-test: $^{**}p <$ 0.02 vs. vehicle-treated rats at normal pressure (n = 6) (−); (B) rats injected with (±)cyanopindolol, in the presence of (±)isoproterenol, (n = 4), U-test: $^{*}p < 0.05$, $^{**}p < 0.02$ vs. vehicle-treated rats exposed to high pressure (-□-), and (C) in rats injected with (±)isoproterenol alone (n = 4): no significant effect was found compared with vehicle experiments at high pressure (-□-).

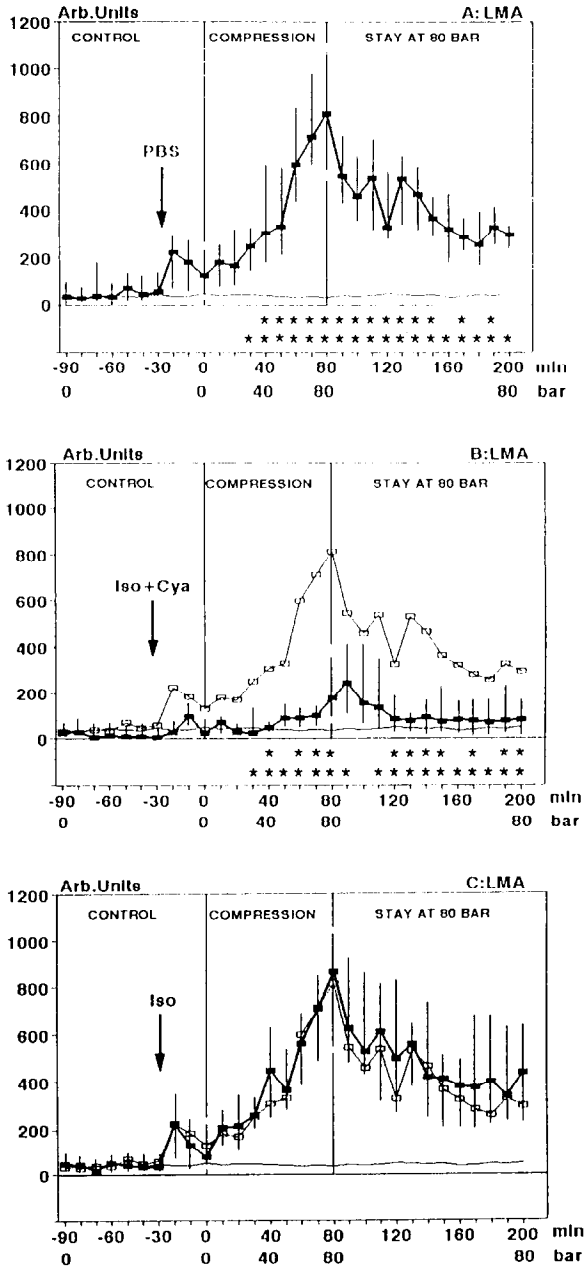

FIG. 4. Development of locomotor and motor activity (LMA) in freely moving rats exposed to 80 bar of high pressure. Y-axis: LMA expressed in arbitrary units using median values ± 25th to 75th percentiles. X-axis: pressure expressed in bar (1 bar = 10^{+5} Pa) and time expressed in minutes. (A) Vehicle-treated rats exposed to high pressure (n = 4), U-test: $^{**}p <$ 0.02 vs. vehicle-treated rats at normal pressure (n = 6) (−); (B) rats injected with (±)cyanopindolol, in the presence of (±)isoproterenol, (n = 4), U-test: $^{*}p < 0.05$, $^{**}p <$ 0.02 vs. vehicle-treated rats exposed to high pressure (-□-), and (C) rats injected with (±)isoproterenol alone (n = 4): no significant effect was found compared with vehicle-treated rats exposed at high pressure (-□-).

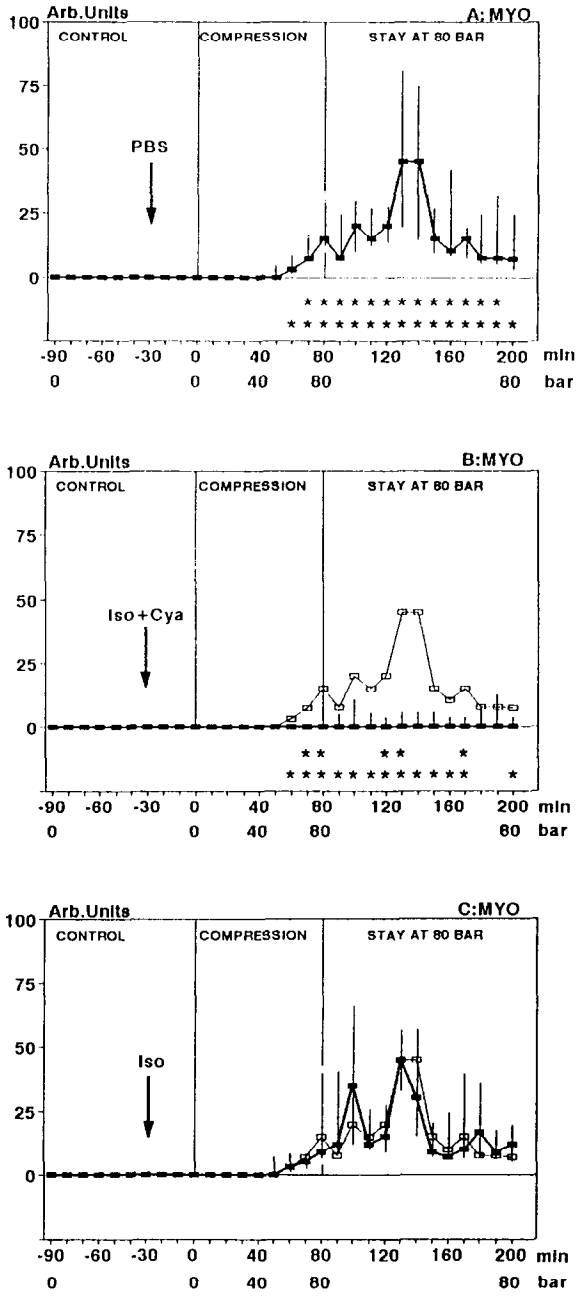

FIG. 5. Development of myoclonia in freely moving rats exposed to 80 bar of high pressure. Y-axis: myoclonia expressed in arbitrary units using median values ± 25th to 75th percentiles. X-axis: pressure expressed in bar (1 bar = 10^{+5} Pa) and time expressed in minutes. (A) Vehicle-treated rats exposed to high pressure (n = 4), U-test: $^{**}p < 0.02$ vs. vehicle-treated rats at normal pressure (n = 6) (−); (B) rats injected with (±)cyanopindolol, in the presence of (±)isoproterenol, (n = 4), U-test: $^{*}p < 0.05$, $^{**}p < 0.02$ vs. vehicle-treated rats exposed to high pressure (-□-), and (C) rats injected with (±)isoproterenol alone (n = 4): no significant effect was found compared with vehicle-treated rats exposed at high pressure (-□-).

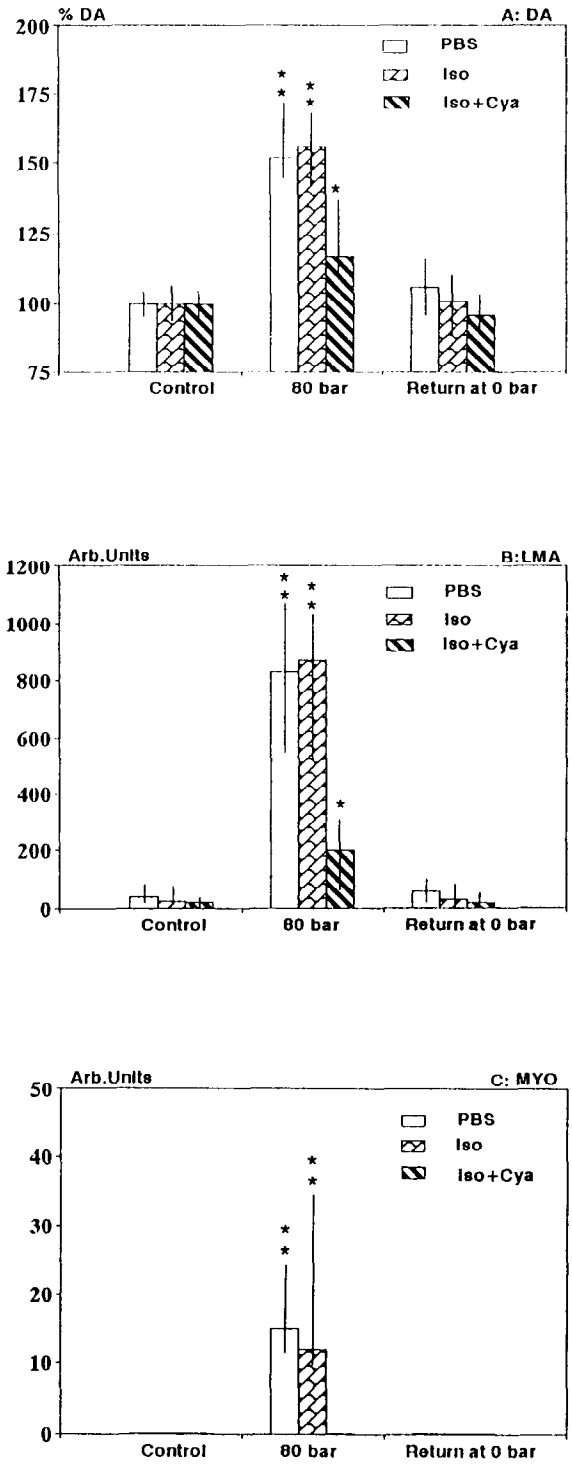

FIG. 6. Histograms representing the value in (A) striatal DA release (B) LMA, and (C) myoclonia in both vehicle- and drug-treated rats at 80 bar and after the pressure had fallen to normal pressure. U-test, $^{*}p < 0.05$, $^{**}p < 0.02$ vs. vehicle-treated rats at normal pressure.

10^{-8} mol (15 μg/kg), and (±)cyanopindolol 2 × 10^{-8} mol (20 μg/kg). (±)Cyanopindolol was generously supplied by Sandoz Ltd. (Basel, Switzerland). CGS 12066B was purchased from Research Biochemicals, and (±)isoproterenol from Sigma (Saint Quentin Fallavier, France).

Data Presentation and Statistical Analysis

Statistical comparisons were made using a Kruskal-Wallis analysis of variance by ranks; following a significant *H* value, post hoc comparisons were made using the Mann-Whitney *U*-test. Drug-induced changes in DA release are expressed as percentage change (positive or negative) relative to the mean of the electrochemical signals recorded before drug administration, during a 70-min period of control before the injection of drug taken as the 100% value (baseline), using median value and the 25th to 75th percentiles.

RESULTS

Experiments at Normal Pressure

At normal pressure, administration of the 5-HT_{1b} receptor agonist CGS 12066B (29,37) was found to produce a significant increase in striatal DA release ($H_1 = 34.7$, $p < 0.001$) (Fig. 2A), which reached a maximal value of +34% compared with the DA basal values. Pretreatment by the 5-HT_{1b} receptor antagonist (±)cyanopindolol, in the presence of (±)isoproterenol, totally blocked the effect of CGS 12066B ($H_1 = 28.8$, $p < 0.001$) (Fig. 2B).

Administration of either 20 μg/kg (±)cyanopindolol, in the presence of 15 μg/kg (±)isoproterenol ($H_1 = 1.3$, NS) (Fig. 2C) or 15 μg/kg (±)isoproterenol administered alone ($H_1 = 0.01$, NS) (Fig. 2D) showed no significant effects upon striatal DA release.

Effect of High Pressure

Compression to 80 bar was found to induce a significant increase in the amplitude of the DA electrochemical response ($H_1 = 29.3$, $p < 0.001$) that reached a maximal increase of +55% during the 2-h period of stay at 80 bar (*U*-test, $p < 0.002$) (Fig. 3A). Administration of (±)cyanopindolol, in the presence of (±)isoproterenol to antagonize binding of (±)cyanopindolol to the β-adrenergic receptors was found partially to block this pressure-induced DA increase in striatal DA release ($H_1 = 24.8$, $p < 0.001$) (Fig. 3B), whereas the administration of (±)isoproterenol alone had no effect ($H_1 = 1.8$, NS) (Fig. 3C).

At the behavioral level, compression was found to lead to a sustained increase of LMA ($H_1 = 29.4$, $p < 0.001$) that reached a maximal value of 837 U (*U*-test, $p < 0,02$) (Fig. 4A), and that progressively decreased during the stay at 80 bar. Administration of (±)cyanopindolol, in the presence of (±)isoproterenol, was found partially to antagonize the development of LMA ($H_1 = 28.4$, $p < 0.001$) (Fig. 4B), whereas (±)isoproterenol administered alone showed no significant effect ($H_1 = 0.09$, NS) (Fig. 4C).

Compression also led to a sustained increase of myoclonia ($H_1 = 21.8$, $p < 0.001$) that reached a maximal value of 45 U (*U*-test, $p < 0,02$) (Fig. 5A) during the 2-h period of stay at 80 bar. Administration of (±)cyanopindolol, in the presence of (±)isoproterenol to antagonize binding of (±)cyanopindolol to the β-adrenergic receptors, was found totally to block the occurrence of myoclonia in rats exposed to high pressure ($H_1 = 21.8$, $p < 0.001$) (Fig. 5B), whereas the administration of (±)isoproterenol alone had no significant effect ($H_1 = 0.8$, NS) (Fig. 5C).

During the decompression phases, all of these behavioral and neurochemical disorders decreased progressively, and reached the control values when the pressure had fallen to atmospheric pressure (Fig. 6).

DISCUSSION

The major finding of the present experiments is that the use of the 5-HT_{1b} receptor antagonist (±)cyanopindolol, in the presence of (±)isoproterenol to antagonize binding of (±)cyanopindolol on β-adrenergic receptors, enables the partial counteraction of both the increase in striatal DA release and the development of LMA, and the suppression the occurrence of myoclonia in rats exposed to high pressure.

During the PBS experiments at high pressure, compression led to an increase in striatal DA release (1,4), LMA, and myoclonia. As previously reported (1,4,32,33) all of these pressure-induced neurochemical and behavioral disturbances progressively returned to control values when the pressure had fallen to normal pressure.

Administration of (±)cyanopindolol in the presence of (±)isoproterenol totally blocked the CGS 12066B 5-HT_{1b} receptor agonist-induced increase in DA release, whereas it only partially antagonized the pressure-induced increase in striatal DA release. Because our data clearly showed that (±)isoproterenol administered alone had no effect on DA release, the present results suggest that the 5-HT neurotransmission could be involved, via an activation of the 5-HT_{1b} receptors, in the increase of striatal DA release at high pressure. This confirms previous data demonstrating that at normal pressure, the 5-HT neurotransmission can modulate striatal DA release via 5-HT_{1b} receptor-mediated processes (8,9,19). However, as (±)cyanopindolol only partially blocked the pressure-induced increase in DA release, whereas it totally blocked the CGS 12066B-induced DA increase, our results further suggest, in agreement with previous studies (1,2), that other neurochemical mechanisms could be involved in the pressure-induced striatal DA release.

At the behavioral level, administration of (±)cyanopindolol in the presence of (±)isoproterenol was found partially to counteract the increase of LMA, and to suppress myoclonia. Because our data clearly showed that (±)isoproterenol had no effect when administered alone, this suggests that the 5-HT neurotransmission could be involved, via an activation of the 5-HT_{1b} receptors, in the occurrence of these pressure-induced behavioral disorders. Support for this may be obtained from previous pharmacobehavioral experiments demonstrating that the inhibition of 5-HT synthesis reduced the severity of the behavioral symptoms in rats exposed to high pressure, whereas the administration of a 5-HT uptake blocker enhanced it (39,40).

However, data obtained from both PBS and (±)cyanopindolol experiments showing that LMA progressively decreased during the 2-h stay at 80 bar, whereas the increase in striatal DA release showed no changes during this period, support as suggested previously (4,5) that the dorsal caudate-putamen is not the main structure of the brain involved in the development of LMA. Elsewhere, the fact that (±)cyanopindolol suppressed myoclonia but only partially reduced DA increase confirms, in agreement with previous studies (4,6), that the occurrence of myoclonia is not related to the pressure-induced increase in striatal DA release. Therefore, the potent effect of the 5-HT_{1b} antagonist (±)cyanopindolol on myoclonia could

be interpreted on the basis of previous experiments suggesting that myoclonia could be the consequence of neurochemical disorders in the lower part of the brain (35), which is well known to include a 5-HT-rich area.

In conclusion, this study demonstrates for the first time, to our knowledge, the existence of interactions at high pressure between the 5-HT and DA neurotransmission. Because the facilitating effect of both 5-HT and 5-HT_{1b} receptor upon the DA neurotransmission has been suggested to be mediated by reducing the inhibitory influence of $GABA_b$ receptors (23), similar mechanisms could be involved at high pressure as the increase in striatal DA release has been equally suggested (1,2) to be mediated by some pressure-induced GABA disinhibition (41). Thus, further neurochemical and behavioral experiments are presently in development in our laboratory to determine whether the effects of 5-HT_{1b} receptors at high pressure are mediated through GABAergic mechanisms.

ACKNOWLEDGEMENTS

This research was supported by Grant DRET 94/140. (±)Cyanopindolol was graciously supplied by Sandoz. B. K. is supported by a fellowship from the Moroccan Government: Ministère de la Pêche Maritime et de la Marine Marchande; J. H. A. is a Research Fellow of la Fondation pour la Recherche Médicale (France).

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