

# Effect of Pressure on the Dopamine Release in Two Selected Lines of Rats: An in Vivo Voltametric Study

[Basıncın Seçilmiş İki Sıçan Türünde Dopamine Salgılanması Üzerine Etkisi: Voltametrik İn Vivo Çalışma]

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## ABSTRACT

When human divers and experimental animals are exposed to high pressure, they develop brain and bio-behavioural disorders. Since it has been demonstrated that pressure exposure increase striatal dopamine release, the present experiments were intended to investigate whether it is viewed as a biochemical manifestation of stress caused by pressure environment or else may reflect the effect of pressure in neurochemical processes. Two genetically selected lines of rats low and high avoidance, which differ drastically in their level of emotionality, were chronically implanted in the nucleus accumbens with multifibre carbon electrodes sensitive to dopamine. Results show that during pressure experiments Roman Low-avoidance rats presented a greater increase in dopamine than Roman High –avoidance rats. These results are discussed in the light of recent experiments in rats exposed to stressful situations or pressure environment. It is concluded that the increase in dopamine release induced by high pressure is not connected to the emotional reaction caused by the introduction of the animals into an unfamiliar environment, as the dopaminergic responses are not those classically observed in stressful situations and therefore could rather reflect the effect of pressure in neurochemical processes.

**Key Words:** Dopamine release; High pressure; Emotional status; Nucleus accumbens; Roman Low-avoidance; Roman High –avoidance

## ÖZET

Dalgıçlar ve deney hayvanları yüksek basınca maruz kaldıklarında beyin hasarı ve biyo-davranışsal bozukluklar geliştirirler. Basıncın etkisi ile striatal dopamin salınımının arttığı saptanmıştır. Bu çalışma gözlenen artışın basınçlı ortamın sebep olduğu stres kökenli bir biyokimyasal oluşum mu yoksa basıncın nörokimyasal işlem üzerine olan etkisi mi olduğunu araştırmayı amaçlamıştır. Genetik olarak seçilmiş ve duygusal açıdan büyük farklılık gösteren düşük ve yüksek sakınlı iki tür sıçanın nucleus accumbens'ine dopamine hassas multifiber karbon elektrotlar yerleştirilmiştir. Sonuçlar, basınç deneylerinde Roman düşük sakınlı sıçanlarının Roman yüksek sakınlılarına oranla daha yüksek dopamin artışı sağladığını göstermiştir. Bu sonuçlar son dönemlerde sıçanların stres koşullarına veya basınç ortamlarına maruz bırakılarak yapılan deneylerin ışığında tartışılmıştır. Stres koşullarında gözlenen klasik yanıt dopaminerjik yanıt değildir. Bu nedenle yüksek basınç uygulamasında gözlenen dopamin salgısındaki artışın hayvanın yabancı bir ortamla karşılaşması ile oluşan duygusal tepkiye bağlı olmadığına kanaat getirilmiştir. Gözlenen artış basıncın nörokimyasal oluşumlar üzerine olan etkisinden kaynaklanıyor olabilir.

**Anahtar Kelimeler:** Dopamin salınımı; Yüksek basınç; Duygusal durum; Nucleus accumbens; Roman düşük sakınlı; Roman yüksek sakınlı

## INTRODUCTION

High pressure is known as a basic aetiological factor underlying central nervous changes referred to as the high-pressure neurological syndrome. This syndrome is observed in both human divers and experimental animals exposed to high pressure of more than 15-20 bars. The main symptoms include electroencephalographic changes and biobehavioral disturbances such as tremor and myoclonia (1). Moreover, data have reported, in divers exposed to very high pressure and/or new breathing mixtures, psychotic disorders such as paranoid thoughts, hallucinations and agitation (2,3). Animals developed various changes in their locomotor and motor activity; and for higher pressure levels than 90 bar convulsive seizures were observed (1).

The electrophysiological, pharmacological and behavioral data obtained from *in vivo* and *in vitro* experiments have indicated various pressure-induced changes in neurochemical process. This includes an increase in both dopamine and serotonin release by the activation of 5-HT<sub>2A</sub> receptors and a decrease of 5-HT<sub>2C</sub> receptors (4). Also, electrophysiological and pharmacobehavioral experiments, respectively, performed in hippocampal brain slices and whole animals, reported at the aminoacidergic neurochemical level that both glutamate-ergic and GABAergic neurotransmission would be altered by pressure. The hippocampal brain slice electrophysiological results suggested that high pressure induced hypersensitivity of NMDA receptors and of a decrease in both GABA inhibition and glutamate release (5).

Accordingly, in response to high pressure exposure have been reported an increase in extracellular dopamine (DA) concentrations in the caudate-putamen (6) and the nucleus accumbens (7). Moreover, the development of locomotor and motor activity disturbances (LMA) were correlated to the pressure-induced DA increase in both the caudate-putamen and the nucleus accumbens (6,7). Those findings indicate a preponderant role of the nucleus accumbens, which is involved in the neuronal control processes of emotion (8,9).

Indeed a number of studies have suggested that the mesocorticolimbic dopaminergic neurons are involved in the control of cognitive processes and emotional behavior. It is also documented that stressful conditions cause a selective activation of dopaminergic neurons projecting to the nucleus accumbens in rodents (10,11). These data indicate that the mesolimbic dopaminergic pathways are activated in response to environmental stimuli.

The neurochemical mechanisms of the pressure-induced DA increase is yet unknown. The increase in nucleus accumbens dopamine metabolism may be interpreted as a biochemical manifestation caused by the pressure per se or an emotional response to a novel situation such as the pressure chamber environment. This is of interest since pressure studies in animals are used to explore the mechanisms of HPNS disorders in humans. However,

in spite of extensive studies devoted to the influence of pressure on the dopaminergic transmission, this factor has yet to be investigated.

In the present paper, we have attempted to evaluate the relationship between the emotional status and the increase of the DA release under high pressure. We have investigated the effects of high pressure on DA metabolism in the nucleus accumbens of two genetically distinct lines of rats (Roman high V- and low V-avoidance), which differ drastically in their level of emotionality (12,13). Initially, RHA/Verh rats and RLA/Verh rats were selected and bred for the rapid acquisition, versus, the non-acquisition, respectively, of a two-way active avoidance response. On the basis of psychogenetic selection has led to considering RLA/Verh rats as being more emotional or anxious than RHA/Verh rats (12,14).

In the present investigation, DA metabolism has been assessed in the nucleus accumbens of freely moving rats by measuring extracellular levels of DA through the use of *in vivo* differential pulse voltammetry with electrochemically pretreated carbon fiber electrodes which enables direct and continuous measurement of the levels of the DA *in vivo* in discrete brain areas of conscious freely moving rats (15,16).

## MATERIALS AND METHODS

### *Animals and surgery*

Experimentally, naive male Roman high avoidance (RHA/Verh) and Roman low avoidance (RLA/Verh) rats weighing 250-300 g were used. They were obtained from breeding colony maintained at the Behavioral Science Institute (Zurich). Rats were housed at  $21 \pm 0.5$  °C in individual altuglass home cages under a 12-12 h light on from 7 a.m to 7 p.m. Food pellets and water were available *ad libitum* in the home cages. Multi-fiber working carbon electrodes were stereotaxically implanted in the nucleus accumbens, under general anaesthesia (pentobarbital sodium 30 mg/kg, i.p and ketamine 100 mg/kg i.m). The reference and auxiliary electrodes (stainless steel screws) were fixed to the bone. The electrodes were attached to a miniconnector, and the whole assembly of electrodes and connector was held in place with dental cement (resin cement, Ivoclar, Switzerland). After surgery; the animals were allowed to recover for one week before being submitted to the pressure experiments. At the end of the experiments, rats were killed. The brain was removed and sliced and the location of the working carbon electrode in the nucleus accumbens was histologically checked referring to the atlas of Koning and Klippel. Brains were stained with Cresyl Violet .

### *Carbon electrodes and electrochemical recordings*

Multi-fibre working carbon electrodes were made from a rod rigid of 10.000 carbon fibres (AGT 4F 10. 000, Carbone Lorraine, France) Sharpened at one extremity

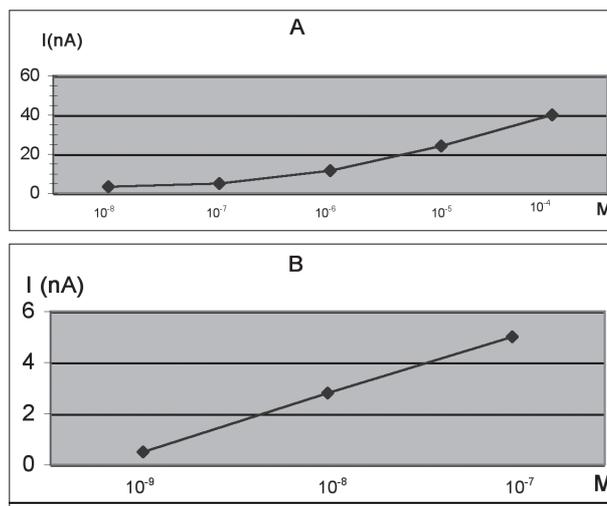
to reduce the external diameter of the electrode from 1 mm to 50  $\mu\text{m}$  at the tip. The entire electrode was encased using an insulating resin and the tip was exposed using an abrasive disc to shape the active surface of the electrode. Before use, the working carbon electrodes were electrochemically pretreated by applying a triangular wave potential of 0-3 v, 70 Hz, 20 s, 0-2 v; 70 Hz, 20 s, 0-1 v; 70 Hz, 15 to increase their sensitivity to DA, as described previously (17).

Voltammetric measurement were performed *in vivo*, as first developed by Kissinger (18), on unrestrained awake animals using differential pulse voltammetry, a PRG5 polarograph (Tacussel, France), and a classical three-electrode potentiostatic system with reference auxiliary and working electrodes. The animals were connected to the polarograph through a flexible cable and a swivel connector; and the polarograph was set up to the following parameters: scan rate 10 or 20 mv/s. Voltage range 0-500 mv or 0-1000 mv/s pulse modulation amplitude 50 mv, pulse modulation duration 48 ms, pulse period 0,2 s. Electrochemical signals were amplified (x 10) and recorded every 3 min; Extracellular DA concentration was quantified automatically by measuring the height of the oxidation peak using a computerized device.

### Electrode calibration

Multi-fibre carbon electrode have been demonstrated to be sensitive for DA as compared with other endogenous compounds such as ascorbic acid (AA), 3,4 dihydroxyphenylacetic acid (DOPAC), homovanilic acid (HVA) and uric acid (UA) by *in vivo* and *in vitro* experiments (15,17,19). However, since it has been demonstrated that these compounds slightly change the amplitude of the electrochemical response of the pretreated multi-fibre carbon electrodes for DA, the electrodes were calibrated *in vitro*, before being implanted, in various solutions of these compounds of  $10^{-8}$  to  $10^{-3}$  M to control their responsibility and their selectivity for DA compared with these compounds.

As previously described, the oxidation peaks for DA and DOPAC both occurred at 160 mV while those of AA, UA and HVA occurred at 90, 300, and 450 mV respectively (15, 17, 19). The height of the voltammograms recorded in DA solutions of  $10^{-8}$  to  $10^{-4}$  M consisted of electrochemical signals that ranged from 3 to 40 nA (Figure 1A). During *in vivo* recordings in awake unrestrained animals, voltammograms were obtained (peak range: 150-180 mV) ranging from 1,5 nA to 4 nA; the corresponding extracellular striatal DA concentration ranged from  $10^{-9}$  to  $10^{-7}$  M (Figure 1B). Elsewhere, multi-fibre carbon electrodes have been clearly demonstrated to constitute a useful tool for electrochemical measurements of DA at pressure since it has been shown: (i) *in vitro*, in a constant DA concentration, that the electrochemical signal was unchanged as pressure increased (20); (ii) *in vivo*, that increasing temperature and oxygen partial pressure has no influence on the DA release (20,21).



**Figure 1.** In vitro and *in vivo* calibration of the multi-fibre carbon working electrode. A: typical electrochemical response during *in vitro* calibration in various solutions of DA, DOPAC, ascorbic acid, HVA and uric acid, ranging from  $10^{-8}$  M to  $10^{-4}$  M. B: *In vivo* amplified (x10) electrochemical responses in awake animals and calibration according to *in vitro* data.

### Exposure to pressure

The free-moving rats were placed in separate altuglass cylinders with food and water and placed in a 50 litter pressure chamber in which the 12-12 h light dark regime was maintained. Rats were compressed to 80 bars of relative pressure with helium, at a rate of 0.1 bar  $\text{min}^{-1}$ . As classically described, oxygen was maintained at a constant partial pressure of 0.4 bar, which is the partial pressure generally used for human divers. The  $\text{CO}_2$  was less than 0.0003 %, humidity was controlled and temperature was progressively increased from 25 to 33  $^{\circ}\text{C}$  to prevent hypothermia because of the important specific heat of helium as compared to air and also for maintaining the comfort of the animals. The stay at the maximal depth lasted 4 h and the decompression 24 h. Animals were decompressed at a rate of 0.006 bar  $\text{min}^{-1}$  from 80 to 12 bar and 0.004 bar  $\text{min}^{-1}$  from 12 bar to atmospheric pressure. During decompression, partial pressure of oxygen was 0.5 bar. All the animals survived to the hyperbaric experiments.

### Ethics and Statistical Methods

All animals received human care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals". Experiments were carried out in accordance with the European Community Council Directive of November 24, 1986 (86/609/EEC). Nonparametric statistics such as the Wilcoxon sign-rank paired t-test (W -test), the Mann Whitney U-test (U-test) and median value  $\pm$  the percentiles were used.

## RESULTS

### Effect of high pressure on dopamine release in the nucleus accumbens of Roman Low-avoidance rats

During the 2 h control period, the DA electrochemical

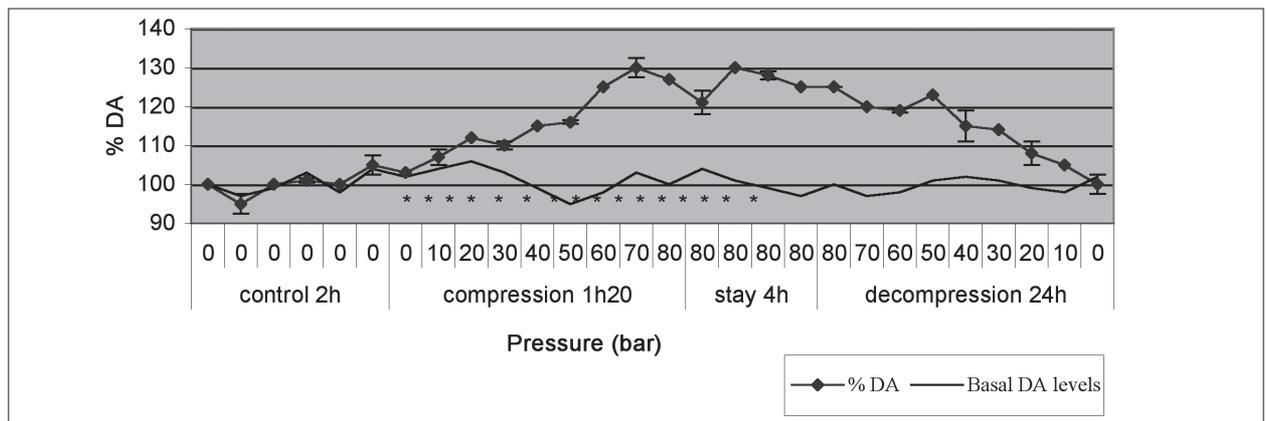
responses showed fluctuations of less than 7 % of their mean values. Compression led to significant increase in DA basal value by 32 % at 80 bar W-test  $p < 0.05$ . During the decompression the DA electrochemical signal decreased and returned to control values (Figure 2).

### ***Effect of high pressure on dopamine release in the nucleus accumbens of Roman High-avoidance rats***

As been observed in RLA rats, during the 2 h control the DA electrochemical response showed fluctuations of less than 7 % of their mean values. Compression significantly led to a sustained increase in DA basal value by 15 % at 80 bar W-test  $p < 0.05$ . During the decompression the DA electrochemical signal decreased and returned to control values (Figure 3).

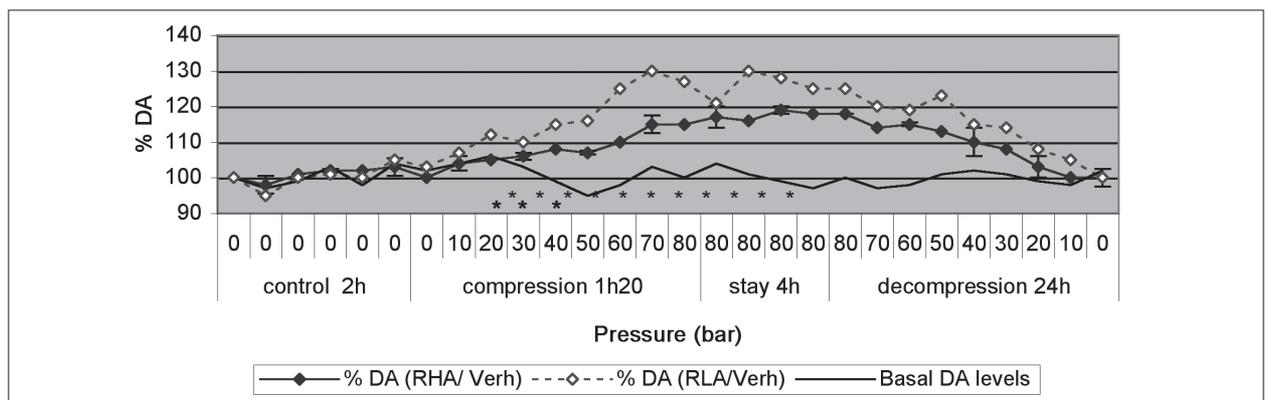
## **DISCUSSION**

The goal of the present study was to assess the significance of the pressure-induced increase in DA release, that has been previously demonstrated during both *in vitro* (22) and *in vivo* (19,20,23) experiments. By analogy with biochemical changes (e.g. activation of those dopaminergic neurons projecting to the prefrontal cortex in the rodent (24,25)) provoked by stress, it has generally been assumed that the pressure-induced increase in DA release represents a neurochemical counterpart of the emotional reaction provoked by the pressure environment. However, our data clearly demonstrated that the increase in DA release was of greater amplitude in RLA/Verh rats than in RHA/Verh rats under high pressure. This did not fit with the classical biochemical situations, as an increase in extracellular



**Figure 2.** Development of the extracellular DA concentration recorded from the nucleus accumbens during pressure experiments in freely moving Roman Low avoidance rats exposed to 80 bar.

Left: compression up to bar, duration 1h20 min. Middle: stay at 80 bar, duration 4h. Right: decompression from 80 bar to atmospheric pressure, duration 24h. Y-Axis, extracellular DA level expressed as a percentage from control value (2h); median values  $\pm$  25th -75th percentiles were obtained from  $n = 6$  rats, X-Axis, pressure expressed in bar, 1 bar = 10<sup>-5</sup> Pascal (P); representation is not proportional to time. W-test: \* $P < 0.005$ .



**Figure 3.** Development of the extracellular DA concentration recorded from the nucleus accumbens during pressure experiments in freely moving Roman high avoidance rats exposed to 80 bar.

Left: compression up to 80 bar, duration 1 h 20 min. Middle: stay at 80 bar, duration 4h. Right: decompression from 80 bar to atmospheric pressure, duration 24 h. Y-Axis, extracellular DA level expressed as a percentage from control value (2 h); median values  $\pm$  25th - 75th percentiles were obtained from  $n = 6$  rats, X-Axis, pressure expressed in bar, 1 bar = 10<sup>-5</sup> Pascal (P); representation is not proportional to time. W-test: \* $P < 0.05$ ; U-test: \* $P < 0.05$  vs. Roman low avoidance rat's data (dotted line).

levels of DOPAC in hypo emotional RHA/Verh rat but not in hyperemotional RLA/Verh rats (13) as well as brain dialysis experiments demonstrated that tail-pinch (TP) and the anxiogenic compounds pentylentetrazol (PTZ) and ZK 93426 increased DA output in the medial prefrontal cortex (PFCX) of RHA/Verh but not RLA/Verh rats (14). Indeed, because RLA/Verh and RHA/Verh rats were placed in the pressure chamber 12 h before pressure exposure to avoid anxious neurochemical response related to a novel environmental situation, i.e., to the pressure chamber environment, our results could therefore, simply reflect, from a neuro-functional point of view, the specific origin of the increase DA release as compared to stressful situation-induced of DA metabolism.

Alternatively, in a previous study, we reported that RLA/Verh rats showed greater behavioral motor disturbances than RHA/Verh rats under high pressure (26). This result also did not fit with the classical behavioural responses of RLA/Verh and RHA/Verh rats in stressful situation, as RLA/Verh rats are very active (13,15). Initially, RHA/Verh rats and RLA/Verh rats were selected and bred for the rapid acquisition, vs. the non-acquisition, respectively, of a two-way avoidance response. On the basis of physiological and behavioural parameters, this process of psychogenetic selection has led to considering RLA/Verh rats as being emotional or anxious than RHA/Verh. Many experiments have clearly demonstrated that systemic administration of either GABA agonist such as sodium valproate or competitive NMDA receptor antagonists such as 2-amino-phosphonoheptanoic acid (2APH) increased the onset pressure of hyperbaric effect (27). During the whole experiments, we have demonstrated in almost 15 years ago that RLA/verh rats presented a greater level of locomotor activities than RHA/verh rats. This behavioural motor disturbances was correlate to the pressure induced DA increase in both RLA ( $r=0.982$ ,  $p<0.001$ ) and RHA ( $r=0.896$ ,  $p<0.001$ ) (28).

At apparent agreement with the present results, the magnitude of the increase in DA release in RLA/Verh seems to correlate better with the capacity of the animal to deal with the pressure rather with the stressful situations. This would be consistent with our hypothesis that the increase in DA release induced by high pressure is not connected to the emotional reaction caused by the introduction of the animals into an unfamiliar environment, as the behavioral and neurochemical responses are not those classically observed in stressful situations, and therefore could rather reflect the effect of pressure in neurochemical processes.

This is the first study, in our knowledge, that demonstrated the influence of the emotional status on the dopamine release in rats exposed to pressure environment. The present findings suggest that the use of RLA/Verh rats and RHA/Verh rats could be of interest for the investigation of the neurochemical and neurological processes underlying the development of the high-pressure neurological syndrome.

## CONCLUSION

The present study demonstrates for the first time of our knowledge that exposure to pressure is associated with an increased DA release in nucleus accumbens in RLA/Verh, but not in RHA/Verh rats. These data are taken together with the lack of correlation between the magnitude of the increased DA release and the spontaneous behavior of animal under high pressure. We proposed that the enhanced DA metabolism associated with pressure reflect activation of the neurochemical processes. The present findings suggest also that the use of RLA/Verh and RHA/Verh rats could be of interest for the investigation of the neurochemical and neurological processes underlying the pressure-induced disorders in dopaminergic neurotransmission and spontaneous behavior. In this field of investigation, neurochemical and pharmacological experiments are presently under development in our laboratory in both RLA/Verh and RHA/Verh rats, to better understand the neurochemical mechanisms of the pressure-induced DA increase.

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