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Evaluation of the effect of chronic exposure to ^{137}Cesium on sleep–wake cycle in rats

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Abstract

Since the Chernobyl accident, the most significant problem for the population living in the contaminated areas is chronic exposure by ingestion of radionuclides, notably ^{137}Cs, a radioactive isotope of cesium. It can be found in the whole body, including the central nervous system. The present study aimed to assess the effect of ^{137}Cs on the central nervous system and notably on open-field activity and the electroencephalographic pattern. Rats were exposed up to 90 days to drinking water contaminated with ^{137}Cs at a dosage of 400 Bq kg^{-1}, which is similar to that ingested by the population living in contaminated territories. At this level of exposure, no significant effect was observed on open-field activity. On the other hand, at 30 days exposure, ^{137}Cs decreased the number of episodes of wakefulness and slow wave sleep and increased the mean duration of these stages. At 90 days exposure, the power of 0.5–4 Hz band of ^{137}Cs-exposed rats was increased in comparison with controls. These electrophysiological changes may be due to a regional ^{137}Cs accumulation in the brain stem. In conclusion, the neurocognitive effects of ^{137}Cs need further evaluation and central disorders of population living in contaminated territories must be considered.

Keywords: ^{137}Cesium; EEG; Open-field activity; Central nervous system; Chronic exposure; Chernobyl

1. Introduction

After the Chernobyl accident, extensive territories were contaminated and a substantial number of people are still subject to chronic exposure from low-level radiation and internal contamination. Byelorussian authors have shown that behavioural disorders and diseases of the central nervous system, such as psychosomatic disturbances, anxiety symptoms, depression, lack of attention and inability to adapt, were frequently observed in humans living in contaminated territories (Kryzhanovskaya, 1997; Titievsky et al., 1997). Some of the neurological signs observed in the Chernobyl victims are similar to those seen with post-traumatic stress syndrome. However, the role of ^{137}Cs in these central effects could be also suggested.

^{137}Cs, a radioactive isoform of cesium, was released into the environment during the Chernobyl accident. ^{137}Cs emits beta particles and gamma rays and its half-life is about 30 years. It can enter the body from food or water. Cesium enters the blood and is carried to all parts of the body, including the central nervous system (Leggett et al., 2003). Some cesium is quickly released

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from the body in the urine, but a part of the absorbed cesium remains in the body for weeks or months (Leggett et al., 2003).

Very few experimental studies have been conducted on the biological effect of ^{137}Cs. The neurological effects have almost never been studied after chronic exposure. One study described disturbances in the metabolism of some neurotransmitters in rats fed with oats contaminated with ^{137}Cs (about 45 Bq kg^{-1}, for 1 month) (Bandazhevsky and Lelevich, 1995). These results were controlled by a similar study conducted in our lab and no effect was observed on rats contaminated with 10 times higher dosages of ^{137}Cs in drinking water (450 Bq kg^{-1}) for 30 days (Houpert et al., 2004).

Since the lack of relevant studies on the effect of ^{137}Cs on the central nervous system, the aim of this study was to evaluate whether exposure to ^{137}Cs in drinking water over a 90-days period, at a dosage similar to that ingested by the population living in contaminated territories (Handl et al., 2003), affected the central nervous system. To achieve this, the locomotor activity, the electroencephalographic (EEG) activity and sleep–wake profiles were measured *in vivo*, in freely moving rats, after chronic ^{137}Cs ingestion at 500 Bq kg^{-1}.

2. Methods

2.1. Animals

Forty-eight Sprague–Dawley male rats (Charles River, France), weighing 367 ± 9 g, were used in the present study. They are divided into "EEG animals" ($n = 24$, with two groups: ^{137}Cs, $n = 12$ and control, $n = 12$) and "behavioural animals" ($n = 24$, with two groups: ^{137}Cs, $n = 12$ and control, $n = 12$).

For "EEG animals", six rats in each group were implanted in order to record their EEG activity. The other six rats in each group were not implanted. Each of these six non-implanted rats were housed with one implanted rat from the same group (exposure or control), in order to prevent isolation and depression.

The rats were housed under standard conditions (22 ± 0.5 °C) with a 12/12 h light/dark cycle (light-on from 8:00 a.m. to 8:00 p.m.). Animals had free access to food and water. Body weight gain, food and water intakes were measured weekly. Animal experiments were approved by the Animal Care Committee of the Institute of Radiation Protection and Nuclear Safety and conducted in accordance with the recommendations of the European Animal Care Commission (Act no. 87-848).

2.2. Exposure

The rats were exposed through drinking water for 90 days. The ^{137}Cs (CERCA, France) dosage was 6500 Bq L^{-1} (*i.e.* 200 Bq day^{-1} per rat, *i.e.* about 400 Bq kg^{-1}), incorporated as chloride.

Control rats drank non-contaminated mineral water.

2.3. EEG analyses

The EEG activity was recorded in freely moving rats by a telemetric system (Data Sciences International, USA), as previously described (Lestaevel et al., 2005). Briefly, after anaesthesia of rat with Imalgene (100 mg kg^{-1}, IM), the transmitter was fixed intraperitoneally and the lead wires were passed under the skin to the skull where EEG electrodes were placed. After a 21-day recovery period, EEG were recorded during sessions of 23.5 h. For each rat, these sessions were performed during the control period (Day 0, just before exposure started) and then during the exposure period (Days 30 and 90). The investigator doing the recordings and analysing data on sleep–wake cycle was blinded to the particular treatment condition. Scoring was carried out manually by a trained observer, assigning three sleep stages: wakefulness (W), slow-wave sleep (SWS) and rapid-eye movement sleep (REM-sleep), as described earlier (Rechtschaffen and Kales, 1968). EEG spectral power was analysed off line using Somnologica software. EEG traces were subjected to a routine fast Fourier transformation (256 points; 50% overlap). The daily spectra were averaged in 10-s epochs and divided into five contiguous bands (0.5–4; 4–8; 8–12; 12–14 and 14–25 Hz).

2.4. Open-field activity

For "behavioural animals" ($n = 24$, with two groups: ^{137}Cs, $n = 12$ and control, $n = 12$), the open-field activity was assessed after 30 and 90 days of ^{137}Cs exposure using an open-field. The methodological details are given elsewhere (Prut and Belzung, 2003). Briefly, each animal was placed individually in the open field (45 cm × 45 cm) monitored by an automated activity monitoring system (Bioseb, France). The distance travelled was recorded over a 20-min period, at 2:00 p.m. ± 2 h. The animals were watched for 20 min only, in order to record open-field activity during the same time of day for all animals (t ± 2 h).

2.5. Cesium measurement

After exposure over a 90-day period, animals were anaesthetized by inhalation of 95% air/5% isoflurane (Forène, Abobott France, Rungis) and killed by intracardiac puncture of blood. After decapitation, the brain was dissected on ice and the hippocampus, striatum, frontal cortex, cerebellum and brain stem were removed. The ^{137}Cs was measured in these structures by gamma spectrometry with a gamma counter (Cobra).

2.6. Statistical analysis

The data were submitted to the overall analysis of variance (ANOVA). When a significant difference between groups was obtained, the results were compared using the

Student–Newman–Keuls post hoc test. Differences were considered to be significant if $p < 0.05$ or $p < 0.01$.

3. Results

3.1. Health parameters and behaviour

Body weight, food intake and water consumption, measured weekly, did not differ significantly between ^{137}Cs-exposed rats and the control throughout the experiment (Table 1).

The open-field activity, assessed by the distance travelled in the open-field, was not significantly modified in exposed rats during 30 or 90 days to ^{137}Cs in comparison with the control (at 30 days, from 4110 ± 742 to 3948 ± 843; at 90 days, from 3617 ± 380 to 3398 ± 277).

3.2. EEG activity and sleep study

During the control period, *i.e.* before ^{137}Cs-exposure commenced, EEG activity and the amount of each wake-sleep phase were similar in the ^{137}Cs and control groups.

No significant differences occurred in the total amount of wakefulness (W), slow-wave sleep (SWS) or rapid eye movement (REM) sleep, analysed over a 23.5-h period, between exposed and control rats after 30 days or 90 days of ^{137}Cs exposure (Table 2).

This lack of effect on amounts of W, SWS and REM-sleep does not signify that there is no effect on the number and the mean duration of episodes. In our experimental conditions, ^{137}Cs exposure decreased the number of W and SWS episodes significantly 30 days after exposure commenced compared with the control, from 465 ± 25 to 367 ± 21 ($p = 0.013$) (Fig. 1). This decrease in the number of W and SWS episodes at Day 30 of exposure occurred similarly during the light and the dark periods (data not shown). ^{137}Cs also increased significantly the mean duration of W episodes (from 1.49 ± 0.14 min to 1.93 ± 0.11 min; $p = 0.03$) and SWS episodes (from 1.33 ± 0.08 min to 1.72 ± 0.12 min; $p = 0.02$) (Fig. 2). After 90 days exposure, these effects disappeared (Fig. 2).

^{137}Cs had no significant effect on the number and the mean duration of REM-sleep episodes after 30 days or 90 days of exposure (Figs. 1 and 2).

3.3. EEG power analysis

After 30 days exposure, no significant effect on the integrated EEG powers of all frequency bands (0.5–4; 4–8; 8–12; 12–14 and 14–25 Hz) of ^{137}Cs-exposed rats was found compared with the control (Fig. 3).

At 90 days exposure, the power of 0.5–4 Hz band of ^{137}Cs-exposed rats increased significantly compared with the control (from 8.80 ± 1.08 to 17.09 ± 2.54 μV^2; $p = 0.04$) (Fig. 3). The integrated EEG powers of other frequency bands were not modified significantly (Fig. 3).

Table 1
Body weight, food intake and water consumption of rats, after chronic exposure to 400 Bq ^{137}Cs kg^{-1}, at Days 0, 30 and 90

Contamination time (days)	Body weight		Food intake		Water consumption	
	Control	^{137}Cs	Control	^{137}Cs	Control	^{137}Cs
0	495 ± 8	491 ± 53	29 ± 1.7	27 ± 1.9	33 ± 1.7	34 ± 2.7
30	566 ± 13	540 ± 41	30 ± 0.9	26 ± 3.1	32 ± 2.6	26 ± 2.4
90	654 ± 19	591 ± 16	29 ± 0.4	30 ± 1.6	30 ± 1.6	31 ± 1.9

Body weight is expressed in g, food intake in g rat^{-1} day^{-1} and water consumption in mL rat^{-1} day^{-1}. Data are expressed as mean ± S.E.M.; $n = 24$ for each group of rats.

Table 2
Wakefulness (W), slow wave sleep (SWS) and rapid eye movement sleep (REM-sleep) amounts in rats sub-chronic exposed to ^{137}Cs (400 Bq kg^{-1} in drinking water), at Days 0, 30 and 90

Contamination time (days)	W		SWS		REM-sleep	
	Control	^{137}Cs	Control	^{137}Cs	Control	^{137}Cs
0	736 ± 25	710 ± 38	570 ± 30	602 ± 40	104 ± 9	97 ± 7
30	682 ± 42	695 ± 20	612 ± 30	620 ± 23	106 ± 9	95 ± 5
90	643 ± 25	593 ± 38	652 ± 8	699 ± 54	115 ± 11	118 ± 15

Data are presented for the 23.5 h of the recording period. Amounts are in minutes. Data are expressed as mean ± S.E.M.; $n = 6$ for each group of rats.

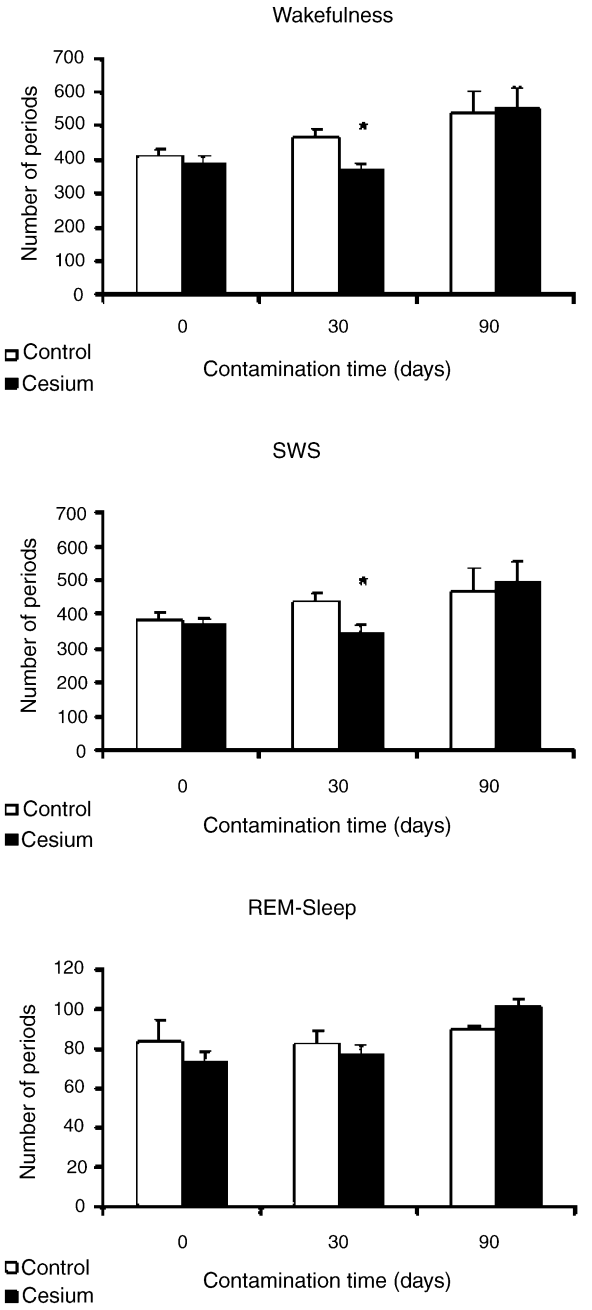

Fig. 1. Number of wakefulness (W), slow wave sleep (SWS) and rapid eye movement sleep (REM-sleep) episodes of rats sub-chronic exposed to ^{137}Cs (400 Bq kg^{-1} in drinking water). Data are presented for the 23.5 h of the recording period. Data are expressed as mean ± S.E.M.; $n = 6$ for each group of rats; *significantly different from control ($p < 0.05$).

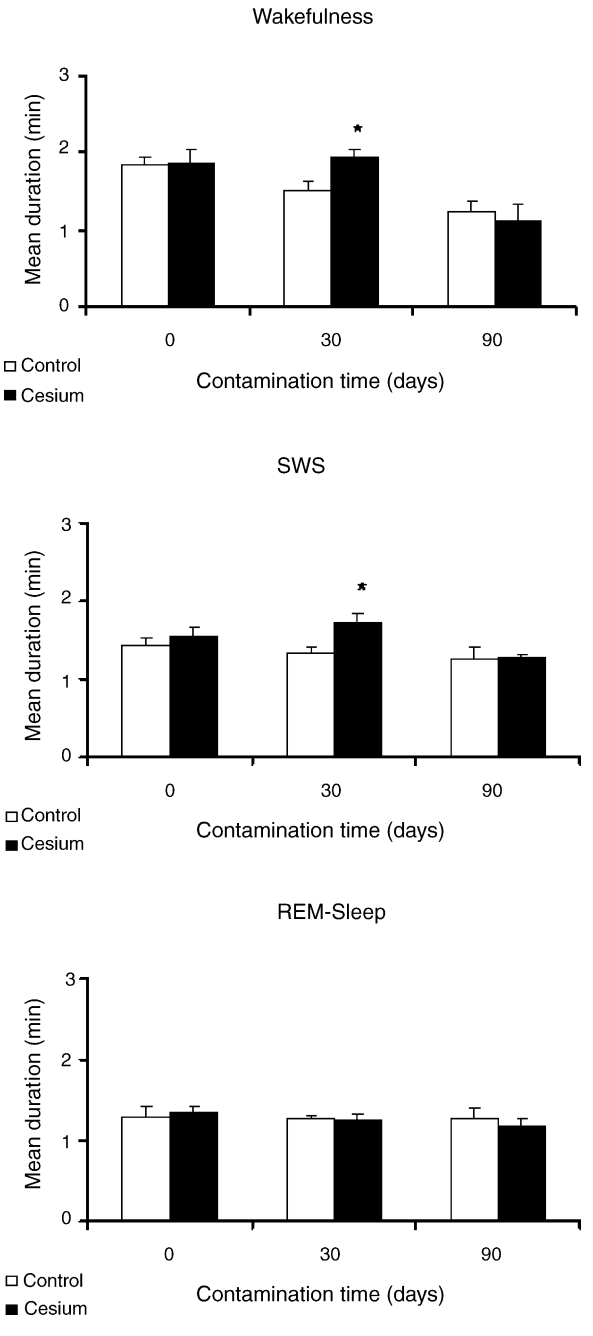

Fig. 2. Mean duration of wakefulness (W), slow wave sleep (SWS) and rapid eye movement sleep (REM-sleep) episodes of rats sub-chronic exposed to ^{137}Cs (400 Bq kg^{-1} in drinking water). Data are presented for the 23.5 h of the recording period. Mean durations of episodes are in minutes. Data are expressed as mean ± S.E.M.; $n = 6$ for each group of rats; *significantly different from control ($p < 0.05$).

3.4. ^{137}Cs measurements

After exposure over a 90-day period, the amounts of ^{137}Cs were 6.05 ± 1.30 Bq g^{-1} for the whole body. For the brain, these amounts of ^{137}Cs were 2.81 ± 0.11 Bq g^{-1} in the frontal cortex, 2.94 ± 0.15 Bq g^{-1} in the hippocampus, 2.94 ± 0.11 Bq g^{-1} in the cerebellum and 3.12 ± 0.18 Bq g^{-1} in the striatum. These amounts

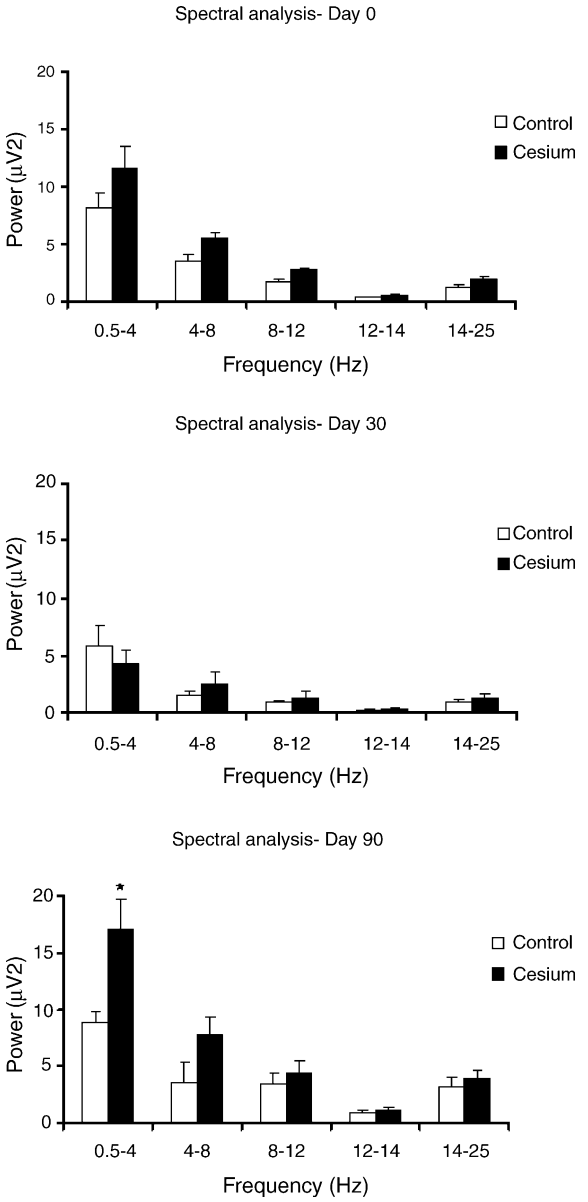

Fig. 3. Spectral evolution of bands power after chronic exposure to ^{137}Cs by drinking water (^{137}Cs, 400 Bq kg^{-1}) at Days 0, 30 and 90. Power is in μV^2. Data are expressed as mean ± S.E.M.; $n = 6$ for each group of rats; *significantly different from control ($p < 0.05$).

of ^{137}Cs did not differ significantly between themselves. On the other hand, the amount of ^{137}Cs in the brain stem (4.26 ± 0.12 Bq g^{-1}) was significantly higher than in other cerebral structures examined ($p < 0.01$).

4. Discussion

This study was carried out to assess the effects of chronic exposure to ^{137}Cs on the central nervous system in adult rats. Body weight, food intake and water consumption were also evaluated as endpoints of general toxicity. There was no significant effect on body weight, water consumption and food intake after ^{137}Cs exposure in our experimental conditions. These results are in line with a previous study that found no significant effect on maternal body weight in mice consuming cesium chloride during gestation and lactation (Messiha, 1988). To our knowledge, no other reports have been published on this subject. However, cesium might have an effect on other physiologic systems, such as the central nervous system, without an effect on overall health.

The potential adverse effects of chronic exposure to ^{137}Cs on the central nervous system in rats have been investigated using EEG activity, which is a particularly sensitive parameter to detect perturbation on the central nervous system (Lestaevel et al., 2005). The data reported here show that chronic ^{137}Cs exposure induces a modification of the hypnogram as early as 30 days of exposure. It consisted of a significant decrease in the number of wakefulness and slow wave sleep episodes, accompanied by a significant increase in the mean duration of these episodes, after 30 days of exposure. These modifications occurred during the light and the dark periods, but had no final effect on daily amount of each sleep stage. This modification of the hypnogram can occur prior to that time, but it was not checked in this study. After 90 days exposure, this effect on the hypnogram disappeared. However, a significant increase in the power of the 0.5–4 Hz band was observed after 90 days of ^{137}Cs exposure compared with controls. The same kind of results on the power of the 0.5–4 Hz band was observed in other experimental conditions. Firstly, a similar result on the 0.5–4 Hz band, obtained after external irradiation, was observed in the prenatally irradiated children, who were born between April 1986 and February 1987, in regions of the Ukraine (Loganovskaja and Loganovsky, 1999). Secondly, the power of the 0.5–4 Hz band increased also after exposure to toluene or morphine (Ghosh et al., 1989; Sala et al., 1995). These results suggest that subtle changes in the 0.5–4 Hz band are a sensitive measure of the effects of ^{137}Cs or other compounds on the central nervous system. Our results suggest also that the duration of exposure plays a role in the electrophysiological perturbations. For episodes duration, compensatory mechanisms would operate at 90 days of exposure, but not during shorter-term exposure. The reverse is observed for bioelectrical activity. These findings agree with previous data already suggesting a link between uranium-induced effects on EEG and the duration of exposure (Lestaevel et al., 2005). Moreover,

a possible adaptive response after chronic exposure to ^{137}Cs could be suggested, as has been already demonstrated (Olivieri et al., 1984). These points must be clarified in the future. Further investigations are also necessary to determine what happens after longer periods of exposure.

The mechanisms by which ^{137}Cs causes these changes on sleep–wake cycle and EEG are unknown. In our study, they are not due to altered health parameters. One possible explanation is a direct effect of ^{137}Cs on the central nervous system. Under our experimental conditions, ^{137}Cs was found in several brain structures of exposed rats during 90 days. Among the cerebral structures examined in the present study, the brain stem has the largest concentration of ^{137}Cs. This result demonstrates that the distribution of ^{137}Cs was not homogenous in the rat brain. This result is in line with previous studies that have also found variation, although different from ours, in the distribution of cesium in areas of the brain, after chronic injection of ClCs (Messiha, 1976, 1984). The brain stem is implicated in wakefulness and slow wave sleep (Jouvet, 1962) and this local accumulation of ^{137}Cs could induce the neurophysiological effects observed. This hypothesis is in accordance with a previous study suggesting that in the clean-up workers, dysfunction of the brain, apparent in the EEG patterns, results from the brain stem damage (Zhavoronkova et al., 1997). A possible mechanism through which ^{137}Cs might be exerting its effects is the link between cesium and potassium. Cesium is a close chemical analogue of potassium. Both potassium and cesium are incorporated into intracellular fluids by active transport mechanisms (Cecchi et al., 1987). Cesium has been shown to compete with potassium for transport through potassium channels and can also substitute for potassium in activation of the sodium pump and subsequent transport into the nervous cell. Further studies are necessary to verify if this link between cesium and potassium could be a possible mechanism to explain its central effects.

These electrophysiological changes could be induced with behavioural effects, themselves linked to disturbances on neurotransmission. Even if both effects are suspected after ^{137}Cs exposure, little is known about this. In the present study, no significant effect was observed on open-field activity after chronic exposure to ^{137}Cs. Even if there is no evidence that sleep patterns and EEG power analysis changes observed in our study would result in neurocognitive changes, similar changes in sleep or EEG power can be correlated with modifications of behaviour in other experimental conditions. For example, pesticides led to a significant increase in the 0.5–4 Hz power band, correlated with alteration of exploratory activity (Timofeeva and Gordon, 2001). Moreover, other experimental studies have shown that chronic exposure to ClCs at high dosage for 14 consecutive weeks increases the spontaneous locomotion activity in mice significantly (Messiha and Krantz, 1973). In another study, rats administered unspecified acute gavage doses of cesium hydroxide exhibited initial signs of hyperexcitability followed by apathy and weakness during the course of 14 days of observation after dosing (Johnson et al., 1975). All these studies could suggest that a correlation between sleep pattern alterations and behaviour is conceivable after ^{137}Cs exposure. In addition to these results on animals, there are many publications concerning the mental health of populations living in radio-contaminated areas after the Chernobyl accident (Havenaar et al., 1997; Kryzhanovskaya, 1997; Gamache et al., 2005). Psychological tests indicated poor attention, lack of concentration, memory impairment and high level of anxiety in adults. After irradiation, clean-up workers, who 20 years ago took part in cleaning the consequences of the Chernobyl disaster, now had organic brain impairments accompanied by mental disorders, such as emotional disorders and memory impairment (Titievsky et al., 1997; Gamache et al., 2005; Kamarli and Abdulina, 1996). These behavioural dysfunctions were observed in line with signs of EEG deficit (Zhavoronkova et al., 1997). In our experimental conditions, additional neurobehavioural studies should be performed to try to correlate EEG changes with behavioural outcomes.

Neurotransmitters play a fundamental role in various neurophysiological processes such as sleep–wake cycle or neurological behaviour. However, a previous study conducted in our lab shown that exposure to ^{137}Cs through drinking water for 30 days at a dosage of 450 Bq kg^{-1} had no significant effect on dopaminergic and serotoninergic metabolism (Houpert et al., 2004). These results are not in line with another experimental study that reports perturbations on the metabolism of serotonin, taurine, alanine, serine, glutamate and glycine, in rats after feeding with oats contaminated with ^{137}Cs for 28 days (45 Bq kg^{-1}) (Bandazhevsky and Lelevich, 1995). These differences could be explained by a different contamination mode (oats *versus* drinking water) and by a different amount of ^{137}Cs (15 Bq rat^{-1} day^{-1} *versus* 200 Bq rat^{-1} day^{-1}). Nevertheless, among metabolisms perturbed in Bandazhevsky's study, some of them play a crucial role in the sleep–wake cycle, such as serotonin, glutamate or glycine (Jouvet, 1996). Complementary studies should be carried out to understand better the role of neurotransmitters on bioelectrical perturbations observed after chronic exposure to ^{137}Cs.

While ^{137}Cs exposure may play a significant role in the occurrence of the health problems observed after the Chernobyl accident, evidence is accumulating that this accident has also induced a significant number of stress-related health problems in the adjacent regions of Belarus, Ukraine and Russia (Havenaar et al., 2003). Stress-related health complaints are a common sequel of toxic disasters and may add to the confusion over possible health consequences, which often follows such events. Psychological factors in the epidemiology of this nuclear disaster are very important and stress-mediated health complaints may outweigh the effects of ^{137}Cs exposure.

In conclusion, these results demonstrated that chronic ^{137}Cs ingestion caused subtle and transient central nervous modifications at electrophysiological level by low perturbations of sleep–wake cycle and EEG activity. The duration of the ^{137}Cs exposure seems to play a role in these effects. These changes may be due to a regional ^{137}Cs accumulation in the brain stem. These electrophysiological modifications could be correlated with changes in neurobehaviour and/or perturbations of metabolism of some neurotransmitters. It will be crucial for people living in the radio-contaminated territories after the Chernobyl accident to determine experimentally if ^{137}Cs exposure could induce similar phenomena after longer periods of exposure and at different exposure levels. Although a great deal of attention is given to the health aspect of the disaster at Chernobyl, the effects of ^{137}Cs on neurocognitive functions is still neglected.

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