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The brain is a target organ after acute exposure to depleted uranium

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Abstract

The health effects of depleted uranium (DU) are mainly caused by its chemical toxicity. Although the kidneys are the main target organs for uranium toxicity, uranium can also reach the brain. In this paper, the central effects of acute exposure to DU were studied in relation to health parameters and the sleep–wake cycle of adult rats. Animals were injected intraperitoneally with 144 ± 10 μg DU kg^{-1} as nitrate. Three days after injection, the amounts of uranium in the kidneys represented 2.6 μg of DU g^{-1} of tissue, considered as a sub-nephrotoxic dosage. The central effect of uranium could be seen through a decrease in food intake as early as the first day after exposure and shorter paradoxical sleep 3 days after acute DU exposure (−18% of controls). With a lower dosage of DU (70 ± 8 μg DU kg^{-1}), no significant effect was observed on the sleep–wake cycle. The present study intends to illustrate the fact that the brain is a target organ, as are the kidneys, after acute exposure to a moderate dosage of DU. The mechanisms by which uranium causes these early neurophysiological perturbations shall be discussed.

Keywords: Depleted uranium; Brain; Paradoxical sleep; Target organ; Kidneys; Toxicity

1. Introduction

Uranium (U) occurs naturally in the earth's crust. It is both a chemical and a radiological toxic element belonging to the actinides group. Depleted uranium (DU) is only slightly radioactive and its toxicity is essentially chemical, like most heavy metals, such as cadmium, mercury or lead (Priest, 2001; McClain, 2002).

The increasing role of U in industrial and military processes has resulted in an increasing occupational exposure to this element. Uranium, after absorption in the gastrointestinal tract or lungs before translocation into the blood, deposits rapidly in the skeleton and kidneys (Priest, 2001). The kidneys are particularly sensitive to the chemotoxic effects of U and are the main target organ with bone (La Touche et al., 1987).

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Although the nephrotoxicity of U has been well documented by experimental studies (Diamond et al., 1989; Zamora et al., 1998; Kurttio et al., 2002; Taulan et al., 2004), few studies have reported the effects of U on the brain. It has been demonstrated that U can cross the blood–brain barrier to accumulate in the brain (Gilman et al., 1998; Pellmar et al., 1999a; Lemercier et al., 2003). This accumulation was not uniform throughout the brain and showed to be dose-dependent (Pellmar et al., 1999a). States of depression or agitation were described in humans after industrial exposure to U compounds (Howland, 1949). More recently, neurocognitive deficits were observed in veterans exposed to DU fragments during the Gulf war (McDiarmid et al., 2000). The health issue of Gulf war veterans has also prompted several animal studies on the neurotoxic effects of DU. Rats that were oral administered 11–717 mg of uranyl acetate kg^{-1} exhibited acute cholinergic toxicity (Domingo et al., 1987). In another study, electrophysiological changes were reported in hippocampal in vitro slices isolated from rats embedded with DU fragments (Pellmar et al., 1999b). Based on these results, it is impossible to conclude whether or not DU has any in vivo biological effect on the brain.

The neurological system is the major target in terms of toxic effects resulting from certain heavy metals, such as manganese, lead and zinc (Brush, 2000). Considering that uranium is also a heavy metal with a chemical toxicity (McClain, 2002), this study aims at evaluating if the brain could be a target organ in the short term (3 days) – as are the kidneys – after acute exposure to DU. A sub-nephrotoxic dosage of DU was chosen seeing that if a central effect of DU does exist, it must occur at least concomitantly with renal alterations, given that kidneys are universally known as the target organ.

2. Methods

2.1. Animals

Thirty-eight male, 10-week-old Sprague–Dawley rats (Charles River, France), weighing 350 ± 20 g, were used. They were divided in three groups; the first group ($n = 10$) was designated for the purpose of biochemical parameters and histology, the second group ($n = 10$) for health parameters and the third group ($n = 18$) for electroencephalographic (EEG) activity and U measurements. In the first group, rats were housed individually in metabolic cages for an 8-day period of acclimatisation. Regarding the two other groups, rats were housed by groups of two in traditional cages. All groups were maintained at a constant temperature (22 ± 1 °C) on a 12-h light/12-h dark cycle (lights-on at 08:00 a.m.) and had free access to food and water. The study was conducted in accordance with French legislation concerning the protection of animals used for experimental purposes. Scientists certified by the French Ministry of Agriculture performed all procedures.

2.2. Contamination

Uranyl nitrate (specific activity: 14×10^3 Bq g^{-1}; ^{238}U: 99.74%; ^{235}U: 0.26%; ^{234}U: 0.001%; Merck, France) was diluted in a saline solution, adjusted to pH 5 with NaOH and filtered. Sixteen rats were intraperitoneally injected with 144 ± 10 μg of DU kg^{-1} in a volume of 200 μl. Sixteen control rats were injected with a saline solution of identical volume and pH.

A sub-nephrotoxic dosage of DU was chosen according to previous results (Houpert et al., 2003).

In order to establish a dose–effect relationship, a lower dosage of DU (70 ± 8 μg DU kg^{-1}) was injected into six other rats. Only two parameters were studied, the sleep–wake cycle and next U measurement at day 3.

2.3. Health parameters, biochemistry and histology

The general health parameters were studied to evaluate the general effect of U on the central nervous system. The body weight gain, food intake and water consumption were measured daily on five contaminated and five control rats.

The sub-nephrotoxicity of DU dosage was checked by the urinary biochemical parameters and histological examination of kidneys. Urine was collected daily on five exposed rats prior to contamination (day 0) and then 24 h (day 1) and 48 h (day 2) after DU injection. The urea, gamma-glutamyl transpeptidase (gamma-GT), glucose and protein levels were measured in these samples according to methods previously published (Giacomini et al., 1981). A histological study was performed at day 2 on five exposed rats used for biochemical parameters and on five control rats. The

right kidney was removed and histological examination was performed in collaboration with Histotox (La Rochelle, France), according to the method previously published (Mitchel and Sunder, 2004).

2.4. Sleep–wake cycle study

The electroencephalographic (EEG) activity was studied seeing that this parameter is particularly sensitive in detecting perturbations affecting the CNS.

A telemetric system, previously described (Vogel et al., 2002), was used to record the EEG activity on freely moving rats (Data Sciences International, USA). This system was implanted 21 days before the exposure of 12 rats—6 exposed and 6 control rats. In brief, under anaesthesia with Imalgene® (150 mg kg^{-1}, i.m.), the implantable transmitter (model TL10M3-F50-EEE) was fixed intraperitoneally and the lead wires were passed under the skin to the skull, where the EEG electrodes were cemented with glue and dental cement (Hesadon, Import Dentaire, France). Each implanted rat was housed with a non-implanted rat in order to avoid isolation.

The data were collected and stored in an acquisition system (Somnologica Software, Resmed, France). Data were collected in a continuous manner for 1 day (day 0) before exposure and 3 days (days 1–3) after exposure. Scoring was done manually, assigning sleep stages to 10 s epochs along a time course of the 23 h and 30 min EEG recording. Three sleep stages were distinguished: wakefulness (W), slow wave sleep (SWS) and paradoxical sleep (PS).

2.5. Uranium measurements

At the end of EEG recording, i.e. at day 3, the rats were anaesthetised by intraperitoneal injection of 500 ml kg^{-1} sodium pentobarbital and exsanguinated in order to try to prevent tissue contamination from blood. The gastrointestinal tract, kidneys, brain and remaining carcass were removed, weighted, mineralised and then analysed for U content by Kinetics Phosphorescence Analysis (KPA) according to the methods previously published (Hedaya et al., 1997).

2.6. Statistical analyses

In terms of health parameters, biochemical parameters and EEG parameters the effect of U was analysed by ANOVA using repeated measurements followed by a Student's *t*-test or paired Student's *t*-test. With regard to U content, results were compared by ANOVA followed by a Student's *t*-test. Differences were considered significant if $p < 0.05$.

3. Results

3.1. Biochemical measurements

Creatinine, glucose and protein excretion in urine was not modified from days 0 to 2. The gamma-GT excretion significantly increased on days 1 and 2, when compared to day 0 (respectively, from 4.6 ± 2.6 to 9.9 ± 2.0 and 13.4 ± 3.3 UI $24\,h^{-1}$, $p < 0.01$) (Table 1). The urea excretion was significantly lower on days 1 and 2 than day 0 (respectively, from 409 ± 87 to 180 ± 91 and 270 ± 63 mg $24\,h^{-1}$, $p < 0.01$) (Table 1).

3.2. Histological examination

Two days after exposure, the epithelium and brush border of the proximal and distal tubules were not injured in rats exposed to DU (data not shown). The

Table 1
Urine biochemical parameters of rats after acute exposure by intraperitoneal injection of 144 ± 10 μg kg^{-1} of DU, at 0 h (day 0), 24 h (day 1) and 48 h (day 2)

Days post-injection	Creatinine	Gamma-GT	Glucose	Protein	Urea
0	12.3 ± 1.0	4.6 ± 2.6	1.1 ± 0.9	8.4 ± 1.9	409 ± 87
1	12.7 ± 0.7	9.9 ± 2.0**	1.0 ± 0.9	10.5 ± 2.1	180 ± 91**
2	11.5 ± 1.8	13.4 ± 3.3**	0.4 ± 0.4	9.8 ± 2.1	270 ± 63**

Creatinine, glucose, protein and urea are expressed in mg $24\,h^{-1}$. Gamma-GT are expressed in UI $24\,h^{-1}$. Data are expressed as mean ± SD; $n = 5$ for each measure.
** $p < 0.01$, significantly different from $t = 0$.

Table 2
Body weight, food intake and water consumption of rats, after acute exposure by intraperitoneal injection of 144 ± 10 μg DU kg^{-1}, at 0 h (day 0), 24 h (day 1), 48 h (day 2) and 72 h (day 3)

Days post-injection	Body weight		Food intake		Water consumption	
	Control	Uranium	Control	Uranium	Control	Uranium
0	321 ± 4.6	316 ± 3.3	25 ± 1.2	23 ± 0.9	32 ± 1.4	27 ± 0.8
1	324 ± 4.7	318 ± 3.7	24 ± 0.8	20 ± 0.2*	35 ± 1.4	34 ± 2.4
2	327 ± 4.2	315 ± 3.7	25 ± 0.5	21 ± 0.5*	31 ± 1.0	31 ± 2.0
3	330 ± 4.9	317 ± 3.7	26 ± 0.8	25 ± 1.0	35 ± 1.3	42 ± 3.1

Body weight is expressed in grams, 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.; $n = 5$ for each group of rats.
* $p < 0.05$, significantly different from control.

glomerules and the vascularisation were also normal (data not shown). An inflammatory infiltrate was absent at this dosage of DU.

3.3. Health parameters

Body weight was not modified from days 0 to 3 (Table 2). Food intake was significantly reduced on days 1 and 2 in exposed rats in comparison to control rats (respectively, from 24 ± 0.8 to 20 ± 0.2 g rat^{-1} day^{-1} and from 25 ± 0.5 to 21 ± 0.5 g rat^{-1} day^{-1}, $p < 0.05$) (Table 2). The daily water consumption did not significantly change from days 0 to 3 in rats exposed to DU, when compared to control rats (Table 2).

3.4. Wakefulness and sleep parameters

Fig. 1 illustrates the periods of time spent in wakefulness, slow wave sleep and paradoxical sleep 23.5 h^{-1} as monitored in control and exposed rats to 70 ± 8 or 144 ± 10 μg kg^{-1} of DU.

No significant effect on the amounts of W, SWS and PS was observed with the lower dosage of DU during 3 days post injection (Fig. 1).

For the higher dosage of DU, the amounts of W and SWS were also not modified from days 0 to 3 (Fig. 1a and b). By contrast, the PS decreased significantly ($-18.5 \pm 3\%$) on day 3 in exposed animals, when compared to control rats (from 70.9 ± 5.8 to 84.0 ± 3.0 min, $p < 0.05$) (Fig. 1c).

The number and mean duration of PS episodes decreased from days 0 to 3, but not significantly (Table 3). The number and mean duration of W and SWS episodes did not change significantly (data not shown).

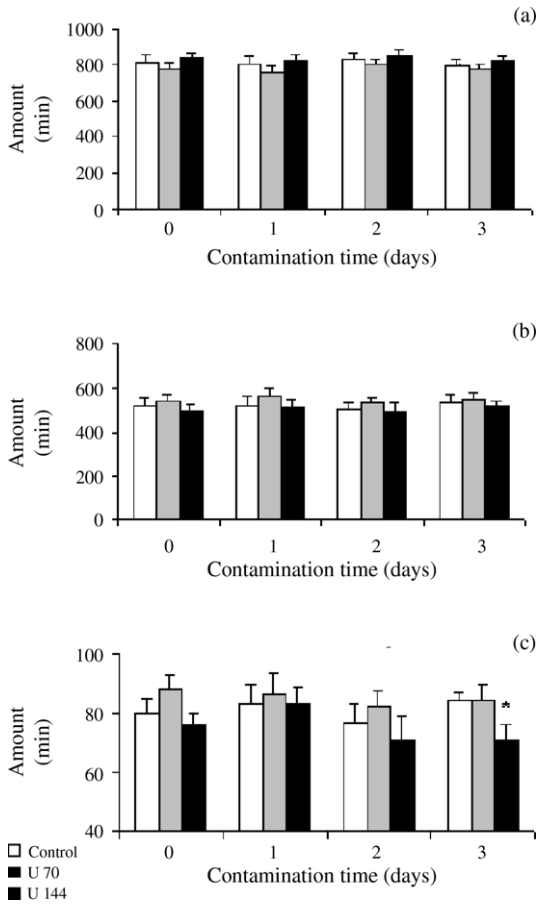

Fig. 1. Wakefulness (a), slow wave sleep (b) and paradoxical sleep (c) amounts after acute exposure by intraperitoneal injection of 70 ± 8 μg DU kg^{-1} (grey columns) or 144 ± 10 μg DU kg^{-1} (black columns). Data for the 23 h and 30 min of the recording period are illustrated. Amounts are expressed in minutes. Data are expressed as mean ± S.E.M.; $n = 6$ for each group of rats; * $p < 0.05$, significantly different from control.

Table 3
Characteristics of PS sleep episodes (number and mean duration) after acute exposure by intraperitoneal injection of 144 ± 10 μg kg^{-1} DU, at 0 h (day 0), 24 h (day 1), 48 h (day 2) and 72 h (day 3)

Days post-injection	Number of episodes		Mean duration of episodes	
	Control	Uranium	Control	Uranium
0	66.2 ± 3.4	71.0 ± 5.3	72.8 ± 4.0	67.0 ± 5.1
1	70.3 ± 3.7	67.3 ± 5.1	71.3 ± 4.5	73.2 ± 4.2
2	68.7 ± 2.3	65.2 ± 3.9	67.0 ± 5.5	65.3 ± 5.6
3	69.8 ± 2.6	66.3 ± 4.9	72.2 ± 2.1	65.7 ± 6.7

Mean durations are in seconds. Data are expressed as mean ± S.E.M.; $n = 6$ for each group of rats. Data are presented for the 23 h and 30 min of the recording period.

Table 4
Levels of uranium, after acute exposure with 70 ± 8 or 144 ± 10 μg DU kg^{-1}, 3 days after intraperitoneal injection, in the kidneys, gastrointestinal tract (GIT), skin and tail, brain and carcass

Groups (μg kg^{-1})	DU at day 3 (ng g^{-1})				
	Kidneys	GIT	Skin + tail	Brain	Carcass[a]
Control	54.7 ± 2.3	501.4 ± 20.2	3.5 ± 0.7	N.D.	0.5 ± 0.1
U 70	909.0 ± 272.8**	589.1 ± 45.7	5.9 ± 1.0	N.D.	18.4 ± 4.8**
U 144	2647.1 ± 741.6**	503.8 ± 9.6	8.7 ± 1.7*	1.3 ± 1.2	35.8 ± 9.6**

Data are expressed as mean ± S.E.M.; $n = 6$ for each group of rats. N.D., no detectable.
[a] Carcass = whole body − (kidneys + GIT + skin + tail + brain).
* $p < 0.05$, significantly different from control.
** $p < 0.01$, significantly different from control.

3.5. Uranium concentrations in tissues

In rats exposed to DU (144 ± 10 or 70 ± 8 μg kg^{-1}), U concentrations in the kidneys, remaining carcass and skin + tail significantly increased in day 3 (Table 4). In the whole brain, traces of U (1.3 ng g^{-1}) were measured on day 3 in exposed rats to 144 ± 10 μg of DU kg^{-1} (Table 4). In the whole brain of rats exposed to 70 ± 8 μg kg^{-1}, DU was not detectable, as was the case for control rats (Table 4).

4. Discussion

In this study, U concentrations administered to rats were sub-nephrotoxic. The quantity of U measured in the kidneys was equivalent to 2.6 μg of DU g^{-1} of kidney 3 days after the injection of DU. A level of renal U equivalent or close to 3 μg U g^{-1} of kidney has been accepted by the U.S. Nuclear Regulatory Commission as a threshold level for acute renal injury (Spoor and Hursh, 1973). The sub-nephrotoxicity of DU dosage used in this study was verified by modifying some urinary parameters, such as gamma-GT and urea excretions. It is well accepted that the increase in the urinary excretion of biochemical parameters or cellular enzymes following exposure to U is a fairly reliable indicator of renal cellular damage (Price, 1982). However, the onset of renal cellular damage induced by U starts generally begins 2–3 days after U administration (Zalups et al., 1988). This apparent latency in terms of the increase in some urinary excretion parameters, such as glucose excretion, is supported by morphological findings. In this study, renal injury was not histologically detectable 2 days after DU administration, which complies with a previous study (Leach et al., 1984).

This sub-nephrotoxicity of DU is also accompanied by a neurological response. A significant decrease in food intake was remarked as early as the first day after injection of DU. This is coherent with previous studies that showed that the earliest parameter for detecting U acute toxicity was food intake, regardless of the U dosage (Domingo et al., 1987; Houpert et al., 2003).

With this sub-nephrotoxic concentration of DU, a significant decrease in PS was observed for the first time on day 3 after DU injection. This decrease was

due to a simultaneous action on the number and mean duration of PS episodes. An indirect effect via the nephrotoxicity of DU could explain this result, since the amount of U in the kidneys was nearing 3 $\mu g\ g^{-1}$ of kidneys, 3 days after injection. Nevertheless, even if U concentration used in this study was sub-nephrotoxic, no correlation was ever established between kidney injury and a decrease in PS. A central effect of DU seems to be the most probable hypothesis to explain this decrease in PS, because U was detectable in the brain 3 days after injection of $144 \pm 10\ \mu g\ DU\ kg^{-1}$. Moreover, with $70 \pm 8\ \mu g\ DU\ kg^{-1}$, U was not detectable in the brain and the concomitantly sleep–wake cycle was not significantly modified.

After the sub-nephrotoxic concentration of DU, the effect on food intake on days 1 and 2 disappears on day 3, with post exposure and the effect on PS occurring on day 3 but not on days 1 and 2. The time course of these phenomena could be explain because U distribution in cerebral structures was heterogeneous (Pellmar et al., 1999a) and it was not the same cerebral structure implicated in food intake and paradoxical sleep, respectively, the hypothalamus and the brain stem. But, even if these two central effects of DU not occur exactly at the same time, a relation between them was shown. Indeed, many neurotransmitters, like dopamine, serotonin and GABA are involved in the regulation of the food intake, but also play a role in the sleep–wake cycle. In this field, a new neuropeptide known as hypocretin could offer some interesting explanations. The neurons with hypocretin have projections in several structures of the CNS that are known to play an important part in the control of food behaviour and rhythm of the sleep–wake cycle, particularly in the regulation of PS (Mignot, 2001). However, even if the link between food intake and sleep has been well studied, the neurobiological mechanisms to explain such an interaction remain still unknown. This also emphasizes the need to evaluate the interaction between uranium and hypocretin.

The results of this study on the central effects of DU are in accordance with previous studies demonstrating that U could enter the central nervous system. Uranium can cross the blood–brain barrier (Gilman et al., 1998). A study with an in situ brain perfusion technique suggested that U could not only transfer into the vascular space but also into the brain parenchyma (Lemercier et al., 2003). It was observed that uranyl acetate administered to mice during a period of 5 days with dietary consumption ad libitum (concentration of U in diet: 0.5%, w/w) accumulated in examined tissues, i.e. liver, kidney and primarily the brain (Ozmen and Yurekli, 1998). In rats implanted with DU pellets, U reached the central nervous system and was distributed heterogeneously (Pellmar et al., 1999a). Previously, it was also demonstrated in vitro that U could induce electrophysiological changes in hippocampus slices isolated from rats embedded with DU fragments (Pellmar et al., 1999b). The renal function parameters were not modified in Gulf war veterans with embedded DU shrapnel in their body in comparison with non-exposed Gulf war veterans (McDiarmid et al., 2000). However, neurocognitive examinations demonstrated a relationship between urine U levels and lowered performance on computerized test assessing performance efficiency (McDiarmid et al., 2000). After 10-years of follow-up however, upon further analysis of individual cases, it was clear that the relationship between the urine U and performance measured was being driven by the two cases with extremely high U values (McDiarmid et al., 2004). Such data raised the possibility that some neurological disturbances occur in the brain, but until now, these neurophysiological changes had not really been explained. If U accumulates in the brain, a local increase of the DU concentration in one area of the brain could induce the neurophysiological effect observed in this study.

The exact mechanism by which U may produce neurotoxicity is unclear. Previous studies have found evidence of oxidation of brain lipids in exposed mice (Briner and Murray, 2005). Lipid oxidation may alter ionic conductance, cell membrane fluidity and other cellular functions. However, mechanisms other than lipid oxidation could be involved. Central sensorimotor deficit observed after exposure to DU could be due to a substitution of calcium by U in the electrophysiological system (Abou-Donia et al., 2002). It has also been demonstrated that prolactin levels were modified in Gulf War veterans injured by DU fragments (McDiarmid et al., 2000). The role of the hypothalamo–pituitary axis in DU neurotoxicity must be considered.

This early neurophysiological perturbation of PS could induce other neurological effects later. PS plays a fundamental role in the memory processes and a decrease in PS could induce an alteration of

the memory capacities (Jouvet, 1994). Neurological deficits have been previously described in men after the Gulf war (McDiarmid et al., 2000). Such neurological deficits are also observed with other heavy metals. The sleep–wake cycle, memory and learning capacities were disturbed after acute exposure with zinc, methylmercury or cadmium, (Tan et al., 1995; Arito et al., 1983; Vataev et al., 1994; Finkelstein et al., 1998; Rodriguez et al., 2003; Leret et al., 2003). These behavioural alterations following acute exposure to heavy metals have been related to hippocampal dysfunction (Altmann et al., 1991). The hippocampus accumulates the divalent metals to a greater extent than other parts of the brain (Stoltenburg-Didinger, 1994). Therefore, the hippocampus is particularly relevant, when it comes to explaining the neurocognitive disturbances observed with U and other heavy metals.

In conclusion, even if the kidney is the critical organ for U acute toxicity, with well-known modifications of urinary excretion parameters, the brain could also be a target organ after acute DU exposure to a sub-nephrotoxic dosage. It could be an organ perturbed at an early stage, with effects at least on health parameters and electrophysiological parameters. These central effects were observed, even though levels of U in the brain were very low. The mechanisms by which U causes these neurophysiological perturbations are currently under investigation in our laboratory. After acute exposure, it is not known if neurological alterations are linked to an indirect effect via its nephrotoxicity or to a central effect of DU. In order to observe if this effect exists with a longer period of exposure at dosages below nephrotoxic concentrations, chronic exposures to U will be required. Such data will provide an evaluation of the U-induced health risk in the case of environmental chronic exposure.

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