

Electrophysiological Changes in Hippocampal Slices Isolated from Rats Embedded with Depleted Uranium Fragments¹

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Abstract: Although nephrotoxicity is considered to be the most serious consequence of uranium exposure, several studies have previously suggested the potential for neurotoxicity. In Operation Desert Storm, U.S. military personnel were wounded by fragments of depleted uranium (DU). This study was initiated to test the potential for DU fragments to cause electrophysiological changes in the central nervous system. Rats were surgically implanted with pellets of DU or tantalum (Ta) as a control metal. After 6, 12 and 18 months rats were euthanized, hippocampi removed and electrophysiological potentials analyzed by extracellular field potential recordings. Six months after implantation, synaptic potentials in DU-exposed tissue were less capable of eliciting spikes (E/S coupling). At 12 months, amplitudes of synaptic potentials were significantly increased in tissue from DU treated rats compared to Ta controls. E/S coupling was reduced. The differences between the electrophysiological measurements in DU-treated and control tissue were no longer evident at the 18 month time point. An analysis of the changes in the synaptic potentials and E/S coupling over the three time points suggests that by 18 months, the effects of aging and DU exposure converge, thereby obscuring the effects of the metal. Since kidney toxicity was not evident in these animals, effects secondary to nephrotoxicity are unlikely. This study raises the possibility that physiological changes occur in the brain with chronic exposure to DU fragments, which could contribute to neurological deficits. ©1999 Intox Press, Inc.

Key Words: Depleted Uranium, Hippocampus, Heavy Metal Toxicity, Synaptic Transmission

INTRODUCTION

The toxicity of uranium has been extensively studied in animal models (Voegtlin and Hodge, 1949; 1953) and the kidney is considered the critical target organ (Leggett, 1989; Diamond, 1989). Although nephrotoxicity is considered the most serious concern of uranium exposure, some reports also suggest the potential for neurotoxicity. Normal mental function was acutely disrupted in three individuals accidentally exposed to a cloud of soluble uranium compounds (Kathren and Moore, 1986). One case study linked the handling of a uranium bar and a subsequent increase in stool uranium with foot cramps, leg pain, and abnormal gait (Goasguen *et al.* 1982). With oral and subcutaneous administration of relatively high doses of uranyl acetate, rats exhibited tremors (Domingo *et al.* 1987). The uranyl ion has been demonstrated to enhance muscle contrac-

tion with acute local concentrations of 200-400 μ M (Lin *et al.* 1988; Fu and Lin Shiau, 1985). These actions were potentiated by low concentrations of extracellular calcium and antagonized by high extracellular calcium (Lin *et al.* 1988). At the neuromuscular junction in the mouse, multiple sites of action were suggested by data demonstrating increased duration of the muscle action potential, increased miniature endplate potentials, and increased quantal content of the endplate potential (Lin *et al.* 1988).

During Operation Desert Storm, U.S. military personnel were wounded by fragments of depleted uranium (DU) (Daxon and Musk, 1993; Daxon, 1993). DU, used in munitions and armament because of its density, is uranium that contains less of the highly radioactive isotope ^{235}U than does natural uranium (0.2% of the total compared to 0.7%). Since surgical removal can produce additional tissue damage, these DU

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fragments were treated as conventional shrapnel and left in place in the wounded soldiers. Uranium bioassays taken over a year after injury indicated that uranium was present in the urine in excess of natural background, up to 30 mg U/l of urine. Recently, our laboratory initiated studies in rats to assess the consequences of chronic exposure to DU fragments (Pellmar *et al.* 1997). In these studies, the low dose of DU exposure produced a level of uranium in the urine that was comparable to the highest seen in the soldiers. As with inhalation and injection, uranium from fragments was found primarily in kidney and bone with excretion through the urine. In addition, unexpectedly, the uranium was found to accumulate in the brain in a dose-dependent manner (Pellmar *et al.* 1999). The present study addresses the electrophysiological changes that occur in the central nervous system in these rats embedded with depleted uranium fragments.

MATERIALS AND METHODS

Male Sprague-Dawley rats were maintained in an Association for Assessment and Accreditation of Laboratory Animal Care International-accredited facility in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 1996). Upon arrival, rats (8-10 weeks of age) were quarantined and screened for diseases. All animals were housed in plastic Microisolator rat cages with hardwood chips as bedding with commercial rodent chow (Harlan, Tekland Rodent Diet #8604, Madison, WI) and water provided *ad libitum*.

Implanted pellets (both DU and tantalum) were approximately 1 mm diameter x 2 mm long. DU pellets (Oak Ridge National Laboratories, Oak Ridge, TN) consisted of 99.25% DU and 0.75% titanium by weight with the uranium isotopes ^{238}U (99.75%), ^{235}U (0.20%) and trace levels of ^{234}U . This is the same DU alloy used in U.S. military munitions. Tantalum (Ta) (Alfa Products, Ward Hill, MA) was used for control pellets because the metal is biologically inert, has a mass similar to uranium, and is frequently used in human prostheses.

Rats were surgically implanted with sterilized DU and/or Ta pellets within the gastrocnemius muscle under anesthesia with ketamine hydrochloride (80 mg/kg) in combination with xylazine hydrochloride (4 mg/kg), given i.p. All surgically implanted rats received 20 pellets of Ta, DU or a combination, 10 pellets in each thigh. Ta controls received 20 Ta pellets; low-dose DU rats received 4 DU and 16 Ta pellets; medium-dose DU rats received 10 DU and 10 Ta pellets; high-dose DU rats received 20 DU pellets. Another set of animals served as non-surgical controls. A total of 15 animals per group were implanted for assessment at 6 and 12 months after implantation. Twenty animals per group were implanted for the 18

month time-point with the expectation of 20-25% natural mortality (Lang and White, 1994; Nohynek *et al.* 1990; Rao *et al.* 1990). Not all rats were used at all time points because of scheduling conflicts with other components of the study. Only one slice per rat was included in the analysis.

Animals were euthanized by decapitation under isoflurane inhalation anesthesia. The brain was quickly removed from the skull and submerged in iced oxygenated artificial cerebrospinal fluid (ACSF). Both hippocampi were dissected out and sliced on a McIlwain tissue chopper (425 μm thick). Tissue was incubated at room temperature in oxygenated ACSF (see below) for 1 hr to allow recovery from the slicing procedure.

A single slice of rat hippocampus was placed in a submerged slice chamber and perfused at a rate of 1-2 ml/min with warmed (30°C) oxygenated ACSF with the following composition (in mM) 124 NaCl, 3 KCl, 2.4 CaCl_2 , 1.3 MgSO_4 , 1.24 KH_2PO_4 , 10 glucose, 26 NaHCO_3 , pH 7.4, equilibrated with 95% O_2 /5% CO_2 . Extracellular recordings were obtained with glass microelectrodes filled with 2 M NaCl placed in *s. radiatum* and *s. pyramidale* of field CA1 to record the population synaptic potential (pPSP) and the population spike (PS) respectively. A stainless steel, concentric, bipolar stimulating electrode was positioned in *s. radiatum* of field CA1 to activate afferents. Constant current stimuli (0.1 - 1.5 mA, 300 μsec) were applied at a frequency of 0.2 Hz. Except when generating input/output (I/O) curves, stimulus current was held constant at an amplitude that elicited approximately 30% maximal response. After placement of electrodes, slices were stimulated at 0.2 Hz for 30 min to allow responses to stabilize. After this equilibration period, I/O curves were generated.

To obtain I/O curves, stimulus intensity was varied from approximately 0.1 to 1.5 mA in 13 steps. Three responses at each current step were recorded and averaged. The 3 I/O curves (stimulus intensity vs. PS, stimulus intensity vs. pPSP, pPSP vs. PS) were analyzed with the data analysis software RS1 (BBN Software Products, Cambridge MA). The responses at each stimulus intensity were averaged for all experiments at each time point. A sigmoid curve was computer fit to the points. To test for significant differences between the averaged curves from DU-treated rats and control rats, the residual sum of squares for the curve fit to the data of each experimental condition was compared with the residual sum of squares for the curve fit to all the data. Significance was accepted at $p \leq 0.05$. Each DU dose was compared to the Ta control for each time point. The I/O curves in the figures plot the average amplitudes \pm the standard error of the mean, with the best-fit sigmoid curve. These techniques to compare I/O relations between animal treatment groups have proved to be an effective approach with previous assessments of *in vivo* treatments (Pellmar and Lepinski, 1993).

Input/Output Curves 6 Months Post-Implantation

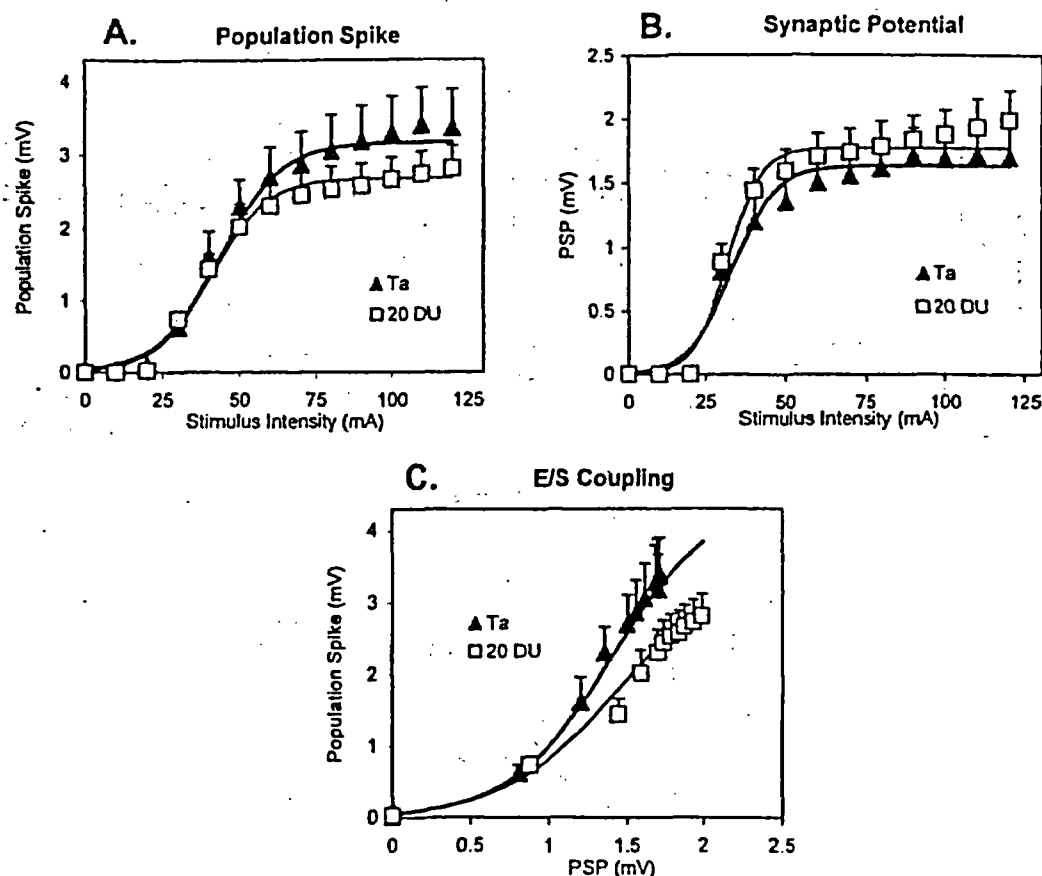


FIG. 1. Input/output curves for hippocampal electrophysiology in rats implanted with depleted uranium (N=9) compared to tantalum controls (N=8), 6 months after implantation of the pellets. Input/output curves were obtained from one slice per animal. Data from all animals were averaged to construct the curves. Error bars represent the standard error of the mean. A: Population spike amplitude was plotted against stimulus intensity. Population spike amplitude was significantly decreased by DU exposure. B: Population synaptic potential amplitude was plotted against stimulus intensity. The population synaptic potential was unchanged with DU exposure. C: Population spike amplitude was plotted against synaptic potential amplitude. A significant decrease in E/S coupling resulted from DU exposure.

RESULTS

Six months after surgical implantation of the pellets, population spikes in field CA1 of the hippocampus of the rats exposed to the high dose of DU were significantly smaller than in the Ta-implanted controls. The input/output curves for the evoked population spike at varying stimulus intensities revealed a decrease in the DU-exposed tissue compared to the unexposed tissue ($P < 0.05$) (Figure 1a). In contrast, the input/output curves for the amplitude of extracellularly recorded synaptic potentials were not statistically different between the two groups (Figure 1b). The input/output relationships reflecting the ability of the synaptic potential to elicit the population spike (E/S coupling) indicated that in the high-dose DU animals this process was significantly impaired ($P < 0.05$) (Figure 1c). The synaptic potential that elicited a half-maximal

population spike calculated from the E/S coupling curve for each individual slice averaged 1.3 ± 0.1 mV in the control animals and 1.7 ± 0.3 mV in the high DU treated animals. This difference did not achieve statistical significance ($P > 0.05$).

Twelve months after pellet implantation, the population spike recorded in the hippocampus of DU-implanted rats was not significantly different from the Ta controls (Figure 2a). In contrast to the 6-month data, the synaptic potential at 12 months was significantly larger in DU-treated tissue than in the controls ($P < 0.05$) (Figure 2b). As at 6 months, E/S coupling was significantly impaired ($P < 0.05$) (Figure 2c). At 12 months, the synaptic potential required to produce a half-maximal population spike was statistically different in DU-treated and control tissue (Ta control: 1.0 ± 0.2 mV; DU: 1.8 ± 0.2 mV). These observations held for all three doses of DU tested. For clarity, only the high and low doses are shown in

Input/Output Curves 12 Months Post-Implantation

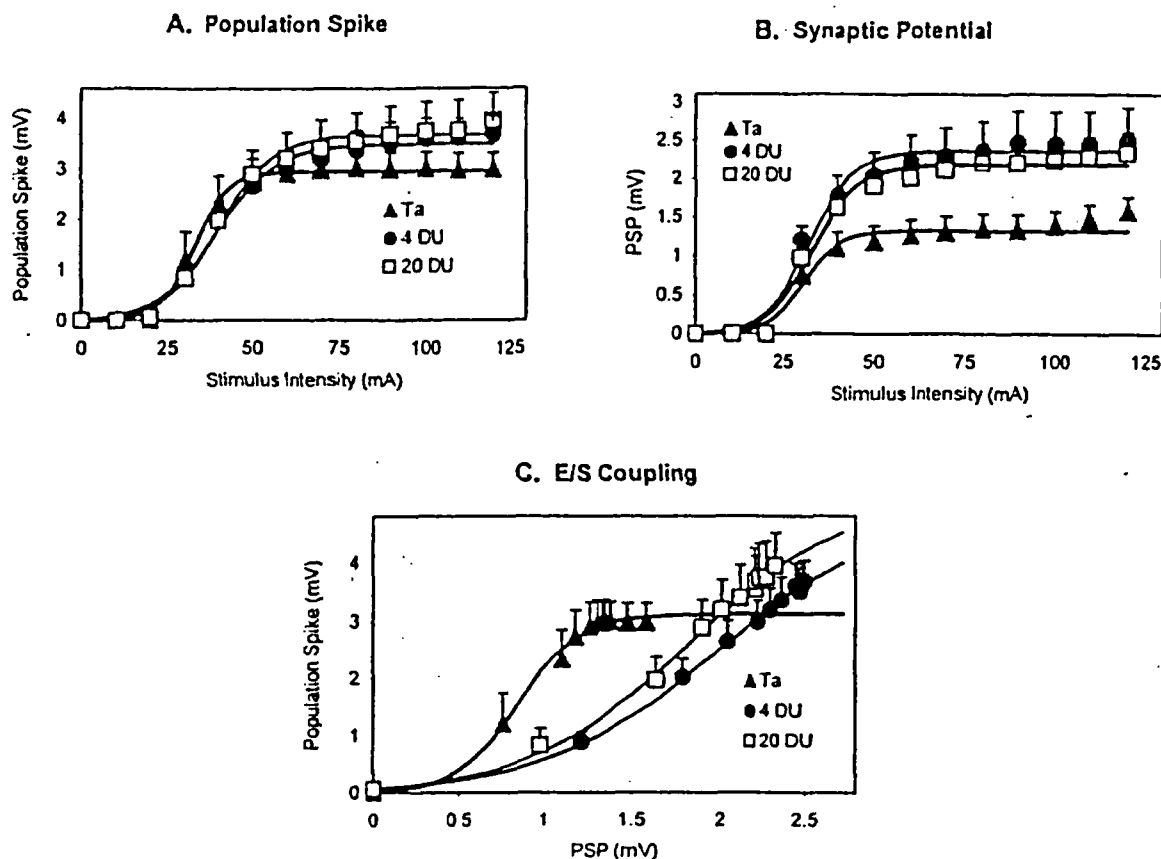


FIG. 2. Input/output curves for hippocampal electrophysiology in rats implanted with depleted uranium compared to tantalum controls, 12 months after implantation of the pellets. Low dose (4 DU pellets; N=9) and high dose (20 DU pellets; N=10) groups were compared to Tantalum controls (N=5). A. No significant differences between the experimental groups were observed for the population spike. B. The synaptic potential was significantly increased with both high and low dose exposures to DU. C. E/S coupling was significantly reduced with exposure to DU.

Figure 2. There was no demonstrable dose dependence to the effects of DU. The changes that occurred with exposure to the low dose were not statistically different from those that occurred with exposure to the high dose. Figure 3 illustrates sample electrophysiological potentials recorded from field CA1 of hippocampal slices excised from rats 12 months after pellet implantation. As indicated by the input/output curves, the extracellularly recorded synaptic potential from the DU-exposed tissue was nearly twice the size of the synaptic potential recorded from the Ta-treated tissue. While the population spike recorded in the DU-treated tissue was larger than in the control tissue, the increase was not proportionate to the increase in the synaptic response.

Eighteen months after the implantation of the metal pellets, the differences between control tissue and DU-treated tissue were no longer evident (Figure 4). Only control and high-dose of DU are shown. For all DU exposures, the input/output curves for the population spike and the synaptic potential were no different from

those for the Ta controls ($P > 0.05$) (Figure 4a,b). E/S coupling also did not differ significantly among the groups ($P > 0.05$) (Figure 4c). The synaptic potential required to produce a half-maximal population spike was 1.7 ± 0.1 mV in the Ta control slices and 1.5 ± 0.2 mV in the high DU treated slices. Eighteen months after implantation of the pellets, uranium content of the hippocampus was significantly greater in the rats implanted with 20 DU pellets compared to the tantalum controls ($P < 0.05$). In DU-treated animals the hippocampus contained 40.4 ± 7.7 $\mu\text{g U/g}$ tissue, while the hippocampus in the Ta controls contained 18.5 ± 6.5 $\mu\text{g U/g}$ tissue.

Although this study was not designed as a longitudinal study to assess the effects of aging, it is instructive to look at the changes in the input/output curves in the Ta controls at the three time points (Figure 5). In the oldest animals (18 months after implantation; 20 months of age), the input/output curve for the elicited synaptic potential is significantly greater than that in the less aged animals (6 and 12 months after implantation; 8 and 14

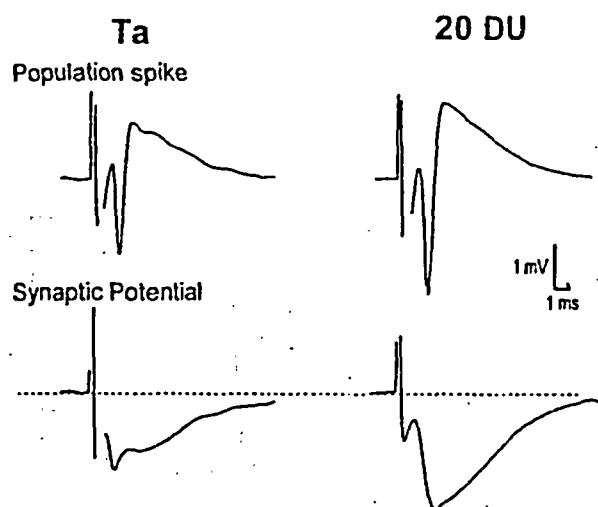


FIG. 3. Electrophysiological potentials from representative hippocampal slices measured 12 months after pellet implantation. On the left are the population spike and the population synaptic potential recorded in a hippocampal slice isolated from an animal implanted with 20 Ta pellets. On the right are the electrophysiological responses from an animal implanted with 20 DU pellets. To facilitate comparisons, the baseline for the synaptic potential is indicated by the dotted line. Notice the larger synaptic potential in the DU-treated tissue. The population spike was not proportionately larger in amplitude indicating less E/S coupling in the DU-treated tissue. Calibration 1 mV, 1 ms.

months of age). Figure 6 illustrates the maximal amplitude of the synaptic potential for slices from Ta control rats and from high-dose DU treated animals for each time point. No differences between the DU and Ta treated animals are evident at 6 months or at 18 months but statistically significant differences exist at 12 months. The maximal amplitudes at 6 months (1.8 ± 0.2 mV for DU; 1.6 ± 0.3 for Ta) are less than those at 18 months (2.1 ± 0.2 mV for DU; 2.2 ± 0.13 mV for Ta). However, the differences in synaptic potential amplitude between time points do not achieve statistical significance ($P > 0.05$).

Using the amplitude of the synaptic potential required to elicit a half-maximal population spike as a measure of neuronal excitability, the changes at each time point are illustrated in Figure 7. The only statistically significant difference between Ta controls and DU-treated tissue is at 12 months when excitability is reduced (required synaptic amplitude is increased) ($P < 0.05$). In the Ta controls, excitability appears to decrease when the animals reach the 18-month time point.

Input/Output Curves at 18 Months Post-Implantation

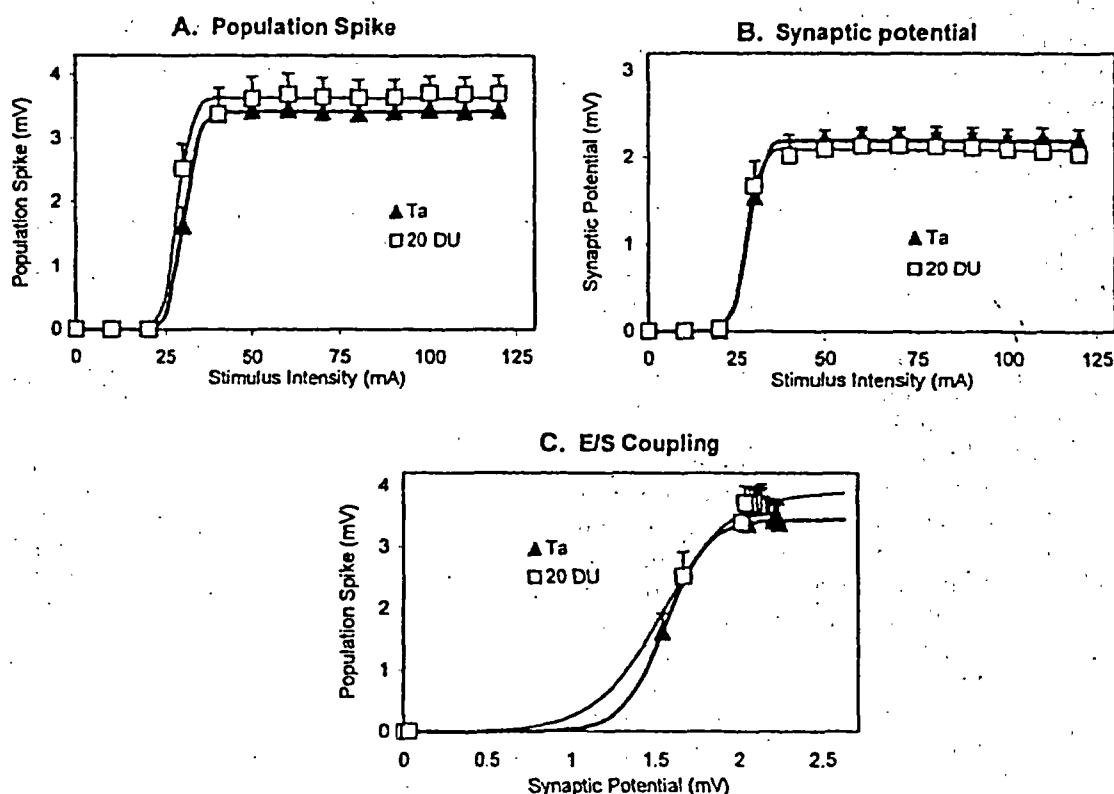


FIG. 4. Input/output curves for hippocampal electrophysiology in rats implanted with depleted uranium (N=12) compared to Ta controls (N=10), 18 months after implantation of the pellets. At this time point, none of the input/output curves showed significant differences between DU and Ta treated tissues. The population spike (A), the synaptic potential (B) and E/S coupling (C) are unchanged by the experimental treatment.

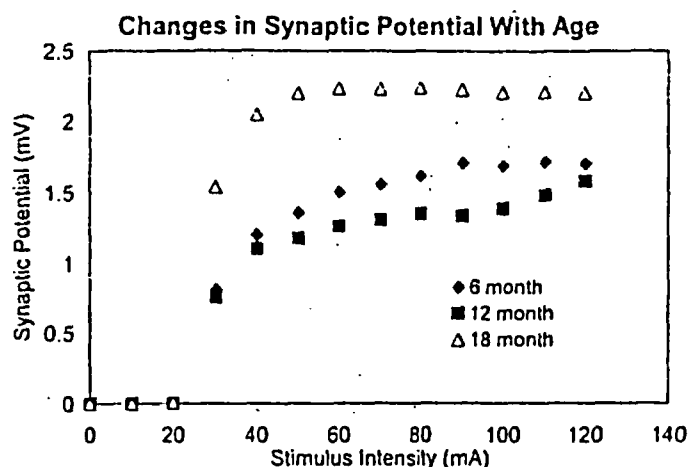


FIG. 5. Input/output curve for the population synaptic potential in the hippocampus of Ta-implanted rats at 6, 12 and 18 months after implantation. These data are replotted from figures 1, 2, and 4 to illustrate the changes that occur in the control animals with age. Notice that 18 months after implantation of pellets (when the animals are about 20 months old) the synaptic potentials are larger than at the 6 or 12 month time points.

DISCUSSION

This study demonstrated that exposure to DU fragments caused neurophysiological changes in the hippocampus. Just six months after implantation, changes in EPSP/spike (E/S) coupling were observed. Synaptic potentials were less effective in producing a population spike in hippocampal slices from DU-treated rats than in slices from untreated controls. Synaptic potentials were not altered by the uranium exposure at this time point. Consequently, the evoked population spikes were smaller in the DU animals than in controls. In animals implanted for 12 months, E/S coupling continued to be altered in the hippocampal slices. However, at this time point the synaptic potential was larger in the DU animals than in controls. As a result, the population spike was not significantly different in the DU-treated tissue. Eighteen months after implantation of the metal fragments, control, and DU exposed tissues were not significantly different from each other.

Although these experiments were not designed as an aging study, it is of interest to examine the changes in the Ta-implanted and DU-implanted tissues over time. The Ta controls were relatively consistent between 6 and 12 months after the surgical implantation of pellets. In the oldest animals, however, the synaptic potentials were larger and E/S coupling was reduced. The amplitude of the synaptic potential required to produce a half-maximal population spike was increased suggesting a decrease in excitability of the neurons. Similarly, Potier *et al.* (1992,1993a) observed an increase in the synaptic potentials elicited in CA1 pyramidal cells by stimulation of *stratum radiatum* of aged Sprague Dawley rats. They

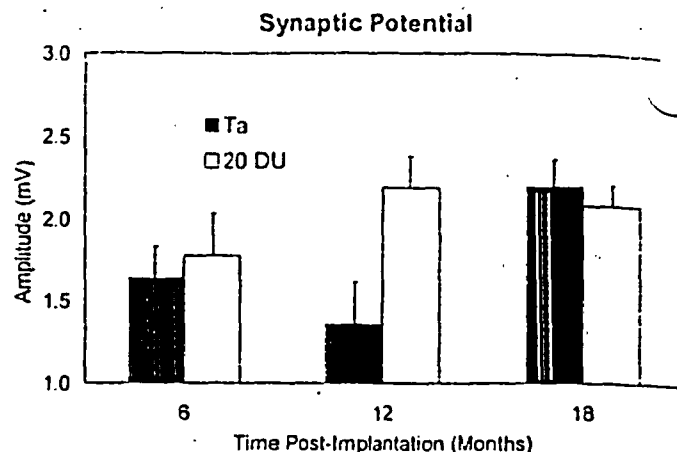


FIG. 6. The maximal amplitudes of the synaptic potential in Ta-treated controls and DU-treated tissue are plotted for the three experimental time points (6, 12 and 18 months after pellet implantation).

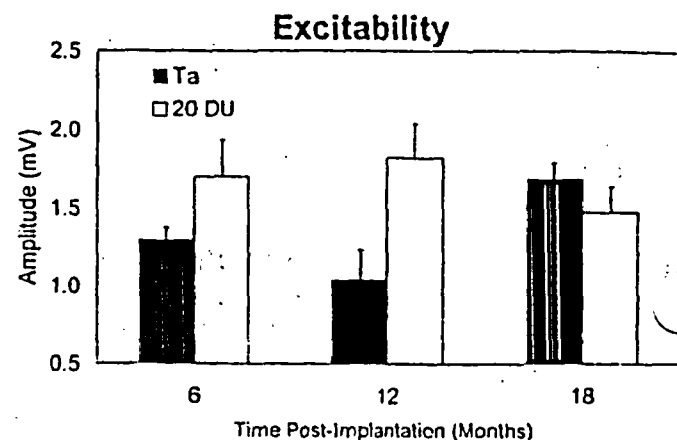


FIG. 7. The amplitudes of the population synaptic potential required to elicit a half-maximal population spike are plotted for the three experimental time points (6, 12 and 18 months after pellet implantation). The larger the amplitude, the smaller the excitability of the tissue.

also noted a decrease in neuronal excitability. These changes are species and strain dependent (Potier *et al.* 1993b) as well as specific to particular synapses. In Fischer 344 rats, Barnes *et al.* (1992) observed that the glutamatergic excitatory synaptic potentials in CA1 of old rats were reduced. In contrast, the synaptic potentials in dentate granule cells from perforant path stimulation were enhanced (Barnes *et al.* 1992, Foster *et al.* 1991). In Wistar rats (Papatheodoropoulos and Kostopoulos, 1996), like in the Sprague Dawley rats, the synaptic potential in CA1 increased in old rats (30 months). In contrast to Sprague Dawley rats, however, neuronal excitability increased, as evidenced by a reduction in the size of the synaptic potential required to elicit a half-maximal population spike.

In light of the agreement between our findings changes with age and those of Potier *et al.* (1992; 1993a) in the same rat strain at the same synapse, it can be argued

that 18 months after implantation the effects of exposure to DU have diminished in comparison to the tantalum controls because the effects of the metal and of age have converged. The uranium exposure resulted in increased synaptic potentials and decreased excitability at 12 months after pellet implantation (14 months of age). By 18 months after pellet implantation (20 months of age), the effects of aging may have produced similar effects, obscuring the consequences of the metal exposure.

The mechanism by which depleted uranium causes the neurophysiological changes is unknown. In these DU implanted rats, kidney toxicity does not appear to be a concern. Despite significant accumulation of uranium in the kidney (5123 ± 259 ng/g with high-dose DU) and excretion in the urine (1009 ± 87 ng/ml with high-dose DU) at 12 months, a preliminary evaluation (Pellmar *et al.* 1997) did not indicate any nephrotoxicity. Even at the high dose of DU, urine lactate dehydrogenase, protein, glucose, N-acetyl- β -glucosaminidase, creatinine clearance and fractional excretion were not altered after 6 and 12 months of exposure. Changes secondary to electrolyte imbalance are, therefore, unlikely. The uranium accumulation in the hippocampus, on the other hand, was significant at 18 months after the pellet implantation, suggesting the possibility of direct effects of chronic uranium exposure in the central nervous system.

Exposure to many heavy metals causes neurotoxicity. For example, lead and aluminum are well-characterized neurotoxins. In adult rats chronically exposed to Pb in the drinking water, synaptic potentials in striatum were unchanged compared to normal controls (Carpenter *et al.* 1994). Chronic lead exposure in adult rats also produced no change in baseline synaptic potential in the hippocampus in field CA1 (Grover and Frye, 1996) or in dentate gyrus (Gilbert *et al.* 1996) even though threshold for long-term potentiation was increased (Gilbert *et al.* 1996). Reports on the effects of chronic exposure to aluminum on synaptic transmission are inconsistent. Synaptic potentials in field CA1 of hippocampus have been reported to decrease (Platt *et al.* 1995), increase (Franceschetti *et al.* 1990), and remain the same (Farnell *et al.* 1985). E/S coupling has been shown to be reduced (Farnell *et al.* 1985). Although the consequences of chronic exposures to aluminum, lead, and uranium are all different, acute exposures at the neuromuscular junction cause remarkably consistent changes. All three metals decreased the endplate potentials (EPP) and increased MEPP frequency (Wang and Quastel, 1991; Cooper and Manalis, 1983; Manalis and Cooper, 1973; Manalis *et al.* 1984; Lin *et al.* 1988; Farnell *et al.* 1985). For lead, it has been hypothesized that the metal enters the terminal through the calcium channel and once internal to the presynaptic terminal can act as a calcium agonist to promote transmitter release (Wang and Quastel, 1991). Disruption of calcium mechanisms is a common action of the heavy metals (Wang and Quastel, 1991; Farnell *et al.*

1985) as well as a response to aging (Campbell *et al.* 1996; Landfield, 1996) that may underlie altered neurophysiological properties.

Changes in the electrophysiological potentials in the hippocampus of experimental animals exposed to DU pellets suggest that behavioral and/or neurological deficits could be a consequence of prolonged exposures in injured soldiers. The Baltimore VA Medical Center, tracking the health of the veterans exposed to DU fragments, has observed a correlation between poor performance on neurocognitive tests and elevated uranium concentration in the urine (Kane *et al.* 1998). In the animal model, preliminary studies monitored locomotor activity, discrimination learning, and a general functional observation battery but did not reveal any gross performance decrements (Pellmar *et al.* 1997). These behavioral measures are not sufficiently sensitive to reveal subtle cognitive deficits. Future studies will evaluate performance on more complex learning tasks. The present study raises the possibility that physiological changes occur in the brain with chronic exposures to DU fragments, which could contribute to neurological deficits. However, any effects of DU must be considered in context of the actions of a known neurotoxin such as lead. Since toxicity from embedded Pb fragments is generally considered to be minimal (Yoshida *et al.* 1995), lead bullets are usually allowed to remain in place. A comparative assessment will be critical to development of therapeutic recommendations for DU fragments.

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