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Brief communication

Can acetylcholinesterase activity be considered as a reliable biomarker for the assessment of cadmium-induced neurotoxicity?

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ABSTRACT

Gonçalves et al. (2012) recently reported the findings of a long-awaited study on the effects of long-term dietary-induced exposure to cadmium (Cd) on the acetylcholinesterase (AChE) activity of adult rodents' brain regions. Their study can be regarded as a significant contribution to the field, as there is paucity of information on the AChE activity in brain regions following exposure to Cd. However, the Cd-induced modulation of AChE activity is an issue surrounded by controversy. We, herein, discuss and summarize the relative in vivo and in vitro experimental data, and set out to answer the straightforward question: can AChE activity be considered as a reliable biomarker for the assessment of Cd-induced neurotoxicity? At this time, we can not answer in the affirmative because of the variation in techniques used and conclusions reached. We make a plea that authors aiming to explore this potential use of brain AChE activity in the future: (a) are aware of the biases that their experimental approach might exert upon this neurochemical parameter, (b) avoid the use of anaesthesia as a mode of sacrifice and clarify its timing, (c) decide upon the use of previously-studied in vivo experimental schemes (so that they can provide comparable results), and finally, (d) identify pharmacological, biochemical and molecular approaches that are appropriate to clarify the implicated mechanism(s) through which Cd modifies AChE activity.

1. Discussion

Gonçalves et al. (2012) recently reported the findings of a long-awaited study on the effects of long-term dietary-induced exposure to cadmium (Cd) on the acetylcholinesterase (AChE) activity of adult rodents' brain regions. The authors studied the changes in the activities of AChE and Na^+, K^+-ATPase in the cerebral cortex, hippocampus, hypothalamus, cerebellum and striatum of adult Wistar rats, following a 5-month (long-term) exposure to an experimental diet supplemented with low-levels of Cd salt (Cd-chloride; $CdCl_2$) or with Cd-contaminated potato tubers (Gonçalves et al., 2012). The authors also assessed the behavioural (cognitive-, motor- and anxiety-related) outcomes following the above-mentioned treatment (Gonçalves et al., 2012). According to our opinion, their study can be regarded as a significant contribution to the field, as there is paucity of information on the AChE activity in brain regions following exposure to Cd (Gonçalves et al., 2010, Pal et al., 1993). We also feel that the experimental protocol used in the aforementioned study (Gonçalves et al., 2012) is exceptionally well designed in order to simulate long-term dietary-induced exposure to Cd.

Gonçalves et al. (2012) concluded that: "*... impaired cognition and enhanced anxiety-like behavior displayed by Cd-intoxicated rats is coupled with a marked increase in the AChE activity and a decrease in the Na^+, K^+-ATPase activity in the brain structures, two important enzymes that can indicate marked alterations in the synaptic transmission*". However, the authors are fully-aware (and rightfully mention this throughout their manuscript) that the Cd-induced modulation of AChE activity is an issue surrounded by controversy. The same authors have actually reported different changes in the AChE activity of brain regions in Wistar rats being exposed to orally-administered Cd (by gavage, every other day, for 30 days) (Gonçalves et al., 2010). With the exception of ecotoxicological studies (that are not particularly focused on Cd), noteworthy publications that report the effects of Cd on brain AChE activity using in vivo experimental approaches, are summarized in Table 1. These include studies on: (a) adult rodents (Carageorgiou et al., 2004, 2005; El-Demerdash et al., 2004; Fasitsas et al., 1991; Gonçalves et al., 2010, 2012; Hrdina et al., 1976; Luchese et al., 2007; Pal et al., 1993; Pari and Murugavel, 2007; Shagirtha et al., 2011; Srinivasan and Ramprasath, 2011), (b) newborn and/or suckling rodents (Antonio et al., 2003; Gupta et al., 1991; Zhang et al., 2009), and (c) other species (fish) (de la Torre et al., 2000; Gill

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Table 1
Overview of the effects of Cd on the brain AChE activity of various species, as reported through in vivo experimental approaches: correlation with the mode of sacrifice.

Reference	Species	Mode of exposure to Cd	Effect on AChE activity[a]	Mode (and time) of sacrifice
Antonio et al. (2003)	– Wistar rat	– Exposure of dams to a solution of $Cd(CH_3CO_2)_2$ (10 mg/L) in drinking water, throughout gestation and lactation	– Non-significantly altered in the Cd-exposed newborn (day 0) rat brains – Significantly decreased in the Cd-exposed 21-day-old offspring rat brains	– Anaesthesia (ether) and then decapitation
Carageorgiou et al. (2004)	– Wistar rat	– i.m. Injections of $CdSO_4$ at a dose of 1 mg/kg (body weight), once daily, for 4 months – i.m. Injection of $CdSO_4$ at a dose of 1, 2 or 5 mg/kg (body weight), once, 8 h before sacrifice	– Significantly increased in the 4-month Cd-treated rat brains – Significantly and dose-dependently decreased in the acutely Cd-treated rat brains	– Decapitation (1 h after last injection of 4-month treatment; authors' archives) – Decapitation (8 h after injection of acute treatment)
Carageorgiou et al. (2005)	– Wistar rat	– i.p. Injections of $CdSO_4$ at a Cd dose of 1 mg/kg (body weight), once daily, for 14 days	– Significantly increased in the Cd-treated rat brains	– Decapitation (1 h after last injection; authors' archives)
de la Torre et al. (2000)	– *Cyprinus carpio*	– Exposure to Cd concentrations of 1.5 to 1.7 mg/L in the experimental aquaria, for 14 days	– Non-significantly altered in the Cd-exposed group's brains	– Anaesthesia (by immersion in ice-cold water for 2–3 min) and then sacrifice by severing the spinal column behind the opercula
El-Demerdash et al. (2004)	– Sprague-Dawley rat	– Oral administration of $CdCl_2$ at 5 mg/kg (body weight), every other day, for 30 days	– Significantly decreased in the Cd-treated rat brains	– Decapitation (time following last administration not specified)
Fasitsas et al. (1991)	– Wistar rat	– i.p. Injection of $CdCl_2$ at a Cd dose of 4 mg/g (body weight), once, 6, 12, 18 and 24 h before sacrifice	– Decreased at 6 and 12 h in the synaptosomal plasma membrane of Cd-treated rats – Increased at 18 and 24 h in the synaptosomal plasma membrane of Cd-treated rats	– Not specified (6, 12, 18 and 24 h after injection)
Gill et al. (1991)	– *Barbus conchonius*	– Exposure to $CdCl_2$ concentrations of 12.6 mg/L in the experimental aquaria, for 48 h	– Significantly increased in the Cd-exposed group's brains	– Decapitation
Gonçalves et al. (2010)	– Wistar rat	– Oral administration of $CdCl_2$ at a Cd dose of 2 mg/kg (body weight), every other day, for 30 days	– Non-significantly altered in the cerebral cortex synaptosomes and striatum of Cd-treated rats – Significantly decreased in the hippocampus, cerebellum and hypothalamus of Cd-treated rats	– Anaesthesia (more than 24 h after last administration)
Gonçalves et al. (2012)	– Wistar rat	– Feeding with normal diet mixed with different amounts of $CdCl_2$ salt dissolved in water (1, 5 and 25 mg/kg), for 5 months	– Non-significantly altered in the cerebral cortex of Cd-treated rats – Significantly increased in the striatum (at all doses), hippocampus (at the 25 mg/kg dose), cerebellum (at all doses) and hypothalamus (at the 5 and 25 mg/kg doses) of Cd-treated rats	– Anaesthesia (more than 24 h after last feeding of the experimental diet)
Gupta et al. (1991)	– Drukery rat	– Exposure of dams to 50 ppm of Cd as $Cd(CH_3CO_2)_2$ in drinking water, throughout gestation	– Non-significantly altered in the Cd-exposed 7- and 14-day-old offspring rat brains – Significantly decreased in the Cd-exposed 21-day-old offspring rat brains	– Not specified
Hrdina et al. (1976)	– Wistar rat	– i.p. Injection of $CdCl_2$ at 0.25 and 1 mg/kg (body weight), once daily for 45 days	– Non-significantly altered in the cerebral cortex of Cd-exposed rats	– By immersion into liquid nitrogen / "near-freezing" technique and then decapitation (after overnight fasting)
Jebali et al. (2006)	– *Seriola dumerilli*	– i.p. Injection of $CdCl_2$ at a Cd dose of 50, 100 and 250 μg/kg (body weight), once, 2 days before sacrifice	– Significantly increased in the Cd-exposed group's brains at the 50 μg/kg dose – Significantly and dose-dependently-decreased in the Cd-exposed group's brains at the 100 and 250 μg/kg doses	– Not specified (2 days after injection)
Luchese et al. (2007)	– Swiss mouse	– s.c. Injections of $CdCl_2$ at 10 μmol/kg (body weight), 5 times per week, for 4 weeks	– Significantly decreased in the Cd-treated mouse brains	– Decapitation (24 h after last injection)
Pal et al. (1993)	– Wistar rat	– i.p. Injection(s) of $CdCl_2$ at a Cd dose of 1 mg/kg (body weight), for 1 week (at an unclear frequency)	– Non-significantly altered in the cerebral cortex, striatum, cerebellum and brain stem of Cd-exposed rats	– Anaesthesia (ether) and then decapitation (after overnight fasting, following 1 week treatment; unclear)

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