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Dosing-time dependent oxidative effects of sodium nitroprusside in brain, kidney, and liver of mice

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ABSTRACT

The purpose of this study was to investigate if the oxidative effects of sodium nitroprusside (SNP) are dosing-time dependent. Therefore, the variation of malondialdehyde (MDA) status was assessed after a single *i.p.* administration of SNP (2.5 mg kg^{-1} b.w.) or vehicle (9‰ NaCl) to different and comparable groups of mice ($n = 48$) at two different circadian times (1 and 13 h after light onset [HALO]). Brain, kidney, and liver tissues were excised over 36 h, and their MDA contents were estimated at 0, 1, 3, 6, 9, 12, 24, and 36 h after SNP administration. *Results:* indicated mean MDA level was not significantly changed in each investigated tissue compared with the control. In contrast, the mean MDA value varied among organs and was comparable in brain and liver but lower than in kidney. The data show SNP significantly ($P < 0.05$) increases MDA status in both tissues and exerts time-dependent oxidative effects with the greatest toxicity coinciding with the beginning of the diurnal rest span (local time: 08:00 h, i.e., at 1 HALO).

The obtained results reveal SNP-induced oxidative damage (evidenced by MDA accumulation) varies according to both the dosing-time and the target organ.

1. Introduction

Nitrovasodilator-SNP ($Na_2[Fe(CN)_5NO]\cdot 2H_2O$) is an excellent drug clinically used for treating acute myocardial infarction (Franciosa et al., 1972), chronic heart failure (Guiha et al., 1974), cardiac (Moffett and Price, 2008), and hypertension emergencies (Gifford, 1959). Several scientific reports (Smith and Kruszyna, 1974; Vesey and Cole, 1985) revealed that SNP in human and other mammalian species undergoes metabolism *in vivo* to release toxic free cyanide (CN^-). Indeed, the lethal effects of CN^- have been known for more than a century and HCN, cyanide salts or cyanogenic compounds have been used in suicides, homicides, and chemical warfare. It is generally believed that *in vivo* the primary pathway for CN^- detoxification is its oxidation to thiocyanate by the enzyme thiosulfate

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sulfurtransferase (rhodanese) that is present in various tissues (Drawbaugh and Marrs, 1987; Sani et al., 2008a,b) and particularly high in liver (Sani et al., 2006a). However, it has been established that the SNP-induced oxidative stress may be due to its ability to release several other potential toxic products such as NO and iron ions (Nazari et al., 2012; Lozinsky et al., 2012; Ibrahim et al., 2012). The molecular mechanism of NO-related SNP-induced neurotoxic effects is not fully understood. Other findings firmly confirmed the hypothesis that biological effects of the exogenous NO donor, SNP, depend on the redox status of the cell (Sokołowska et al., 2003). Therefore, the cytotoxicity of SNP was attributed to enhanced ROS production, which in turn resulted in decrease in antioxidant levels. Nevertheless, it has been demonstrated that oxidative stress is a main mediator in NO-induced neurotoxicity and apoptosis in human cells in a concentration and time-dependent manner (Zhang and Zhao, 2003). These concerns have hindered the general enthusiasm in using SNP in the management of acute hypertension emergencies, even though its potency, rapid onset, and short duration of action. However, there is nowadays the resurgence of interest in the use of SNP, particularly in the management of acute decompensated heart failure (Mullens et al., 2008; Opasich et al., 2009) and in the prediction of blood pressure during certain cardio-vascular surgical procedures (Roitberg et al., 2008; Spielberg et al., 2014; Zhao et al., 2014). Although the increased usefulness of SNP in several cardio-vascular diseases cares, prolonged use of SNP has often been associated with the risk of its end-products toxicity on brain, kidney, and muscle of patients (Guo et al., 2013; Moerman et al., 2013). Therefore, there is a great necessity to discuss possible strategies by which the safety and efficacy of SNP as part of the treatment regimen for hospitalized heart failure patients might be improved.

Time-of-day of exposure is rarely considered in the study of desired (efficacious) and nondesired (toxic) effects of drugs. In rodents, the nephrotoxicity of heavy metal (Hg, Cd) as well as that of some antibiotics (amikacine, dibekacine) exhibits large amplitude circadian rhythms, with a peak located at the rest span and a trough at the activity span (Cal et al., 1986; Cambar et al., 1987). It seems, therefore, that a temporal relation may be observed between the circadian variation in MDA and chronotoxic effects of some agents, respectively, in the liver and kidney. Our previous data revealed that the neurotoxic effects of SNP varied markedly within the 24-h period depending on the time of administration (Sani et al., 2011). The circadian variation in drug effects are suggested not to be due to rhythmic changes in the pharmacokinetics of drugs but rather to an endogenous rhythm in drug susceptibility resulting from a circadian rhythm controlled by an inner clock (Moore and Eichler, 1972). It would be expected that the drug concentration as well as the dosing-/sampling-time would affect both the efficacy and the toxicity of an antihypertensive drug. However, little is known about the time-of-day dependence of either measured levels of neuronal toxicity or lipid peroxidation induced by SNP. Such information would be of importance to both exercise scientists and clinicians, since it would help to minimize the drug-induced side effects by a better optimization of drug use at the adequate time-of-day. Thus, the dosing of medication at the targeted biological time with reference to circadian rhythms can result in modulation of its toxicity (Hrushesky et al., 1989). To this end, the oxidative effects of SNP could be dependent on the period of waxing and waning of motor activity. Therefore, the purpose of this study was to assess if time-of-day of exposure influences the oxidative effects of SNP in terms of its effects on MDA production in the brain, kidney, and liver of mice.

2. Materials and methods

2.1. Animals and housing

Animals used in this study were *Swiss albino* mice obtained from the Central Animal House (SIPHAT, 2013 Foundouk-Choucha, Tunisia) at 9 weeks of age (≈25 g body weight) and experiments lasted from June to November 2007. The animals were housed 4–5 per cage with free access to food and water. They were acclimated for at least 3 weeks prior to and during each study (Reinberg and Smolensky, 1983), to controlled conditions of temperature (22 ± 2 °C), relative humidity (50–60%), and 12-h light: 12-h dark photoperiod (light on at 07:00 h). The desired synchronization of mice was documented by the quantification of normal circadian rhythmicity in rectal temperature, the acrophase (peak time) used as marker rhythm index. In this study carried out at the FSB Toxicometry and Chronobiometry Laboratory (Bizerte, Tunisia), all experimental procedures conformed to the NIH recommendations and current guidelines (Portaluppi et al., 2008).

2.2. Drug

SNP ($Na_2[Fe(CN)_5NO]\cdot 2H_2O$) brown–red powder was kindly supplied by the National Laboratory of Drug Control (1006 Tunis, Tunisia). The SNP is a chemical product of synthesis that is hydrosoluble but little soluble in alcohol. Based on our previous experience with SNP in chronotoxicological studies, in adult mice neurotoxic effects of SNP were triggered with doses raging from 2.5 to 5 mg · Kg^{-1}-a median toxic dose TD_{50} (dose inducing 50% motor-inco-ordination) equal to 3.6 ± 0.5 mg · Kg^{-1}. Since oxidative effects of SNP are seemed to be related to its neurotoxicity, the lowest neurotoxic SNP dose (of 2.5 mg · Kg^{-1}) was used to investigate SNP-induced oxidative damage. Thus, the solution was freshly prepared each experiment day by adding an adequate volume of sterile distilled water to obtain the 2.5 mg/kg concentration of SNP. That single dose was administered to mice in a fixed fluid volume (10 mL · Kg^{-1} b.w.).

2.3. Study designs and tissue samplings

The study design is summarized in Table 1. A total of 192 synchronized male mice were randomly assigned to four groups (48/group) for treatment with SNP (2.5 mg · kg^{-1}) or sodium chloride (0.9%). The first two groups of animals were treated once with an i.p. injection of saline (group 1) or SNP (group 2) at a fixed local time (08:00 h, i.e., at 1 HALO), whereas the two last groups were similarly dosed with saline (group 3) or SNP (group 4) at later 12 h (20:00 h local time, e.g., 13 HALO). Each dosing-time involved different but comparable