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# Arsenic reduces the antipyretic activity of paracetamol in rats: Modulation of brain COX-2 activity and $CB_1$ receptor expression

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ABSTRACT

We examined whether subacute arsenic exposure can reduce paracetamol-mediated antipyretic activity by affecting COX pathway and cannabinoid $CB_1$ receptor regulation. Rats were preexposed to elemental arsenic (4 ppm) as sodium arsenite through drinking water for 28 days. Next day pyrexia was induced with lipopolysaccharide and paracetamol's (200 mg/kg, oral) antipyretic activity was assessed. The activities of COX-1 and COX-2, the levels of $PGE_2$, TNF-α and IL-1β and expression of $CB_1$ receptors were assessed in brain. Arsenic inhibited paracetamol-mediated antipyretic activity. COX-1 activity was not affected by any treatments. Paracetamol decreased COX-2 activity, levels of $PGE_2$, TNF-α and IL-1β and caused up-regulation of $CB_1$ receptors. Arsenic caused opposite effects on these parameters. In the arsenic-preexposed rats, paracetamol-mediated effects were attenuated, while $CB_1$ receptor up-regulation was reversed to down-regulation. Results suggest that elevated COX-2 activity and reduced $CB_1$ expression could be involved in the arsenic-mediated attenuation of the antipyretic activity of paracetamol.

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## 1. Introduction

Paracetamol (Acetaminophen) is an extensively used non-steroidal anti-inflammatory drug (NSAID) for treating fever and pain. Paracetamol reduces prostaglandin (PG) synthesis in CNS (Ayoub et al., 2011), indicating inhibition of cyclooxygenase (COX) activity. Paracetamol displayed 4-fold selectivity for COX-2 inhibition and a standard dose caused almost complete COX-2 inhibition in humans, whereas only moderate COX-1 inhibition was observed (Hinz et al., 2008). COX-1 seems to have no role in febrigenesis (Blatteis, 2006; Hopkins, 2007), while the proposed mechanism of hypothermia through COX-3 inhibition was rejected (Hinz et al., 2008; Kis et al., 2005; Li et al., 2008). Thus, its antipyretic effect is attributed to COX-2 inhibition in brain, particularly hypothalamus (Graham and Scott, 2005; Li et al., 2008). Recently, Engström Ruud et al. (2013) demonstrated that paracetamol reduced lipopolysaccharide (LPS)-induced fever by inhibiting COX-2 and not by inhibiting microsomal prostaglandin-E synthase-1 (mPGES-1).

Paracetamol's pharmacodynamics could also be mediated through interactions with the endocannabinoid system (Hogestatt et al., 2005). p-Aminophenol, the deacetylated metabolite of paracetamol, conjugates with arachidonic

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acid in CNS to form N-arachidonoylphenolamine (AM404; Bertolini et al., 2006). AM404 prevents uptake of endogenous cannabinoid anandamide, causing increase in anandamide level. Anandamide produces antinociceptive and hypothermic actions through $CB_1$ receptors (Howlett, 1995). This pathway could account for paracetamol's antipyretic effect (Oscier et al., 2007). $CB_1$ receptors are heterogeneously distributed within CNS (Pertwee, 2008), where hypothalamus is particularly enriched with these receptors (Tsou et al., 1998). Activation of $CB_1$ receptors, besides causing analgesia, decreases body temperature and plays pivotal role in signaling mechanisms that promote fever response (Fraga et al., 2009). Further, Staniaszek et al. (2010) suggested that the effects of COX-2 inhibition are mediated by cannabinoid receptor activation.

Groundwater contamination with arsenic is a major public health problem worldwide, including severely affected populations of the Indian subcontinent. The WHO permissible limit of arsenic in drinking water is 10 μg/L and FAO permissible limit for irrigation water is 100 μg/L (Rahaman et al., 2013). However, the range of arsenic concentrations found in natural waters around the world varied from <0.5 μg/L to >5000 μg/L (Rahaman et al., 2013). In the Indian subcontinent, the maximum arsenic concentration in the groundwater was found around 3.7–4.7 ppm (Chatterjee and Chatterji, 2010). But there is report that in West Bengal, India, people were exposed to arsenic-contaminated water even in the range of 50–14,200 μg/L (Guha Mazumder and Dasgupta, 2011).

Arsenic is an established human carcinogen; also causes various health hazards (Argos et al., 2012; Chen et al., 2011). Arsenic produces inflammation or exacerbates inflammatory states (Bunderson et al., 2004; Chen et al., 2007). Arsenic modulates inflammatory response depending on the magnitude and duration of exposure (Wu et al., 2003). Acute and subchronic arsenic exposure exacerbated inflammatory process and nociceptive behavior in mice and rats (Aguirre-Banuelos et al., 2004; Aguirre-Bañuelos et al., 2008), which were attributed to exacerbated COX-derived $PGE_2$ release.

Medical or self administration of NSAIDs is quite common in the world, where millions of people are getting exposed to arsenic through contaminated drinking water. Recently, we demonstrated that the repeated exposure to arsenic through drinking water reduced the therapeutic efficacy of the nonselective COX inhibitor ketoprofen in rats (Ahmad et al., 2012). As the findings have potential clinical relevance for therapeutic application of NSAIDs in people of the arsenic-affected areas, we desired to extend the study to paracetamol. We evaluated whether subacute exposure to arsenic can reduce the antipyretic effect of paracetamol in rats; also whether the reduction occurs along with alterations in the COX pathway and $CB_1$ receptor regulation.

## 2. Materials and methods

### 2.1. Chemicals

Lipopolysaccharide (LPS), sodium-m-arsenite (94%) and paracetamol (99%) were purchased from Sigma Chemicals (USA). Carboxymethyl cellulose sodium salt (CMC) was purchased from G.S. Chemical Testing Lab and Allied Industries, Bombay. The EIA kits for assessing cyclooxygenase (COX) activity and production of pro-inflammatory mediators $PGE_2$, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) were procured from Cayman Chemicals Company (Ann Arbor, MI). Revertaid First strand synthesis kit for cDNA synthesis was purchased from Fermentas Life Sciences, Luisiana, while Quantitect SYBR Green PCR Master mix from Qiagen, Germany. All other chemicals used were of analytical grade.

### 2.2. Dose/concentration selection

We reported earlier a concentration–response relationship between arsenic given through drinking water and ketoprofen by oral gavage in rats (Ahmad et al., 2012). We found that the magnitude of inhibition of the effects of ketoprofen with arsenic exposure for 28 days was statistically similar for 4 and 40 ppm, while the 0.4 ppm did not alter the effects of ketoprofen. We, therefore, selected the arsenic concentration as 4 ppm, which is an environmentally relevant groundwater contamination level too (Chatterjee and Chatterji, 2010).

The dose of paracetamol for the antipyretic study was selected from the exploratory study, where paracetamol at 200 mg/kg dose completely inhibited the LPS-induced pyrexia after 3 h of paracetamol administration, while 300 and 400 mg/kg doses caused hypothermic response. So we selected 200 mg/kg b.w. as the dose for the present study. And according to Reagan-Shaw et al. (2008), its human equivalent dose is about 32 mg/kg. For a 60–70 kg human, it comes to 1920–2240 mg/day, which is within the range of the dose recommended for adult humans, i.e., 1000–4000 mg of paracetamol per day. As per Reagan-Shaw et al. (2008), the Human equivalent dose (mg/kg) = animal dose (mg/kg) × animal Km/human Km, where the Km factor is the value of body weight (kg) divided by body surface area ($m^2$). The respective Km factors for rat and adult human (60 kg b.w.) are 6 and 37.

### 2.3. Animals and experimental design

Adult male Wistar rats (110–130 g) were obtained from the Laboratory Animal Resource Section of the Institute. They were kept in polypropylene cages and maintained on pellet feed (Amrut Feeds, Pranav Agrorochemicals and Feeds, New Delhi). The feed and water were given *ad libitum*. Prior to commencement of the experiments, animals were kept in the laboratory conditions for a minimum period of 7 days for acclimatization. The animals were handled and the study was conducted in accordance with the Institute guidelines for the protection of animal welfare.

Rats were exposed to elemental arsenic (4 ppm) as sodium arsenite through drinking water for 28 days. A single dose of paracetamol (200 mg/kg b.w.) was administered in an aqueous suspension of 0.25% carboxymethyl cellulose (CMC) by oral gavage at a predetermined time on the 29th day. The rats were fasted for 16–18 h prior to paracetamol administration, but water was provided *ad libitum*. Rats were divided randomly into 6 groups of 6 each. Control rats were given distilled water (Group I). Group II was given equivalent amount of CMC on the 29th day (vehicle control). Rats of Group III were given LPS @ 1.8 mg/kg b.w. at a predetermined time on the 29th day for

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