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Early exposure to electrophilic ambient pollutant causes vascular and cardiac changes by activating transient receptor potential channels

A. G. Soares[1], J. Florenzano[1], L. Rodrigues[1], S. A. Teixeira[1], S. D. Brain[2], M. N. Muscará[1], S. K. Costa[1]. [1]Pharmacology, ICB/USP, Sao Paulo, BRAZIL, [2]Cardiovascular Division and Pharmacology & Therapeutics, King's College London, London, UNITED KINGDOM.

Introduction: Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide [1]. Importantly, the adverse effects of short or long exposure to ambient pollution on health correlates with numbers of cardiovascular-associated deaths and/or hospital admissions [2]. Particulate matter (PM) is composed of substances that cause health concerns, but there is still limited understanding of the effects on its organic contaminants (e.g. quinones). We showed that transient receptor potential (TRP) channels (V1) mediate lung inflammation induced by diesel exhaust particle and 1,2-Naphthoquinone (NQ) [3]. We hypothesised that the early exposure to 1,2-NQ acts as a critical link between PM-induced CVDs at youth and TRPV1/4 channels activation as an important underlying mechanism.

Method: Neonate male mice were exposed to 1,2-NQ (100 nM, 15 min) or its vehicle on days 6, 8 and 10 of life (Ethics Committee of São Paulo University number 48/2016). After 33 days, mice were euthanised and the chronotropism and vascular reactivity to adrenergic and cholinergic stimuli alone or in presence of TRPV1 (capsazepine, CZP) or TRPV4 (HC067047) antagonists were assessed in isolated right atria and pulmonary artery. Data is presented as mean ± SEM, n=5. Stats were performed by ANOVA plus Bonferroni's test. $P<0.05$ was taken as significant.

Results: Concentration response curves to norepinephrine (NE) in vehicle or CZP group elicited no difference in E_{max} responses in the atria of young mice after prior exposure to 1,2-NQ (VEH: 259±27, 1,2-NQ: 218±12, CZP: 313±42 and 1,2-NQ+CZP: 242±9 bpm). Effects of NE on pD_2 value from atria of 1,2-NQ-treated mice was attenuated (5.7±0.1*) compared to vehicle-treated mice (6.6±0.1), and TRPV1 blockade reversed this effect (7.2±0.1*). Exposure to 1,2-NQ did not affect the negative chronotropic indices or pD_2 to carbachol. The pD_2 artery response to phenylephrine (7.6±0.1) from 1,2-NQ-exposed mice is higher than vehicle (6.7±0.06*), and TRPV1 or TRPV4 blockade potentiated this effect (8.2±0.1# and 7.6±0.1#, respectively). Exposure to 1,2-NQ enhanced endothelium-dependent artery relaxatation (E_{max} 69±1.0*) to acetylcholine compared to vehicle (46±0.4), which was blocked by CPZ (14±1.0#) and HC067047 (38±3.0#).

Conclusion: We show for the first time that 1,2-NQ exposure during the postnatal period exerts significant changes in atria rhythm and artery reactivity at youth. This is triggered by a mechanism involving activation of TRPV1/TRPV4. The TRP blockade might offer new strategies for management of pollution-induced CVDs.

References: [1]WHO Top 10 causes of death, http://www.who.int/mediacentre/factsheets. [2]Newby et al (2015). Eur Heart J 36:83-93b. [3]Costa et al (2010). Arch Toxicol 84(2):109-17.

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