Old Dog, New Tricks: Oral Dosing Hypertensive Rats with Anti-Inflammatory Agent Colchicine Gives Vascular Remodeling and Function Recovery

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In the USA, resistant uncontrolled hypertensive patients express an increased risk of mortality when compared to untreated hypertensive patients.1 The current pharmacopeia of hypertensive medication therefore fails to ameliorate resistant hypertension and poses a risk to the health of patients, highlighting the need for new drugs and a change in approach to how we treat hypertension.

Colchicine, a microtubule polymerization disruptor, is currently in use for its anti-inflammatory properties in the treatment of gout. Recently, work from our laboratory indicates a role for colchicine in vascular function recovery within arteries from hypertensive animals by preventing retrograde trafficking of key components of vascular reactivity.2,3 The long-term in vivo consequences of colchicine treatment within the context of animal models of hypertension remains unclear however. The aim of this project was to determine the effect of colchicine dosing on the key hallmarks of hypertension including blood pressure, vascular function and vascular remodeling.

11-16 week old Wistar Kyoto (WKY) and spontaneously hypertensive rats (SHR) were bred and purchased from Janvier Labs, France, for tandem in vivo and in vitro experiments.

In vivo: Under general anesthesia (isoflurane), animals were fitted with abdominal telemetric devices which allowed for continual recording of blood pressure and body temperature. Animals were orally dosed with either placebo (PBS), or Colchicine (0.05mg/kg, in PBS) once daily for 4 weeks. Differences in blood pressure were determined by recordings generated for 1hr prior to dosing. In week 1, acute changes in blood pressure were determined by a 2hr recording post dosing.

In vitro: changes in vascular function via isometric tension recordings of 3rd order mesenteric arteries (MAs). Concentration effect curves were generated in response to vasoconstrictors methoxamine (α-1 adrenoreceptor), U46619 (TXA2), 5-HT and KCl from basal tone, and vasorelaxant isoproterenol (β-adrenoreceptor), sodium nitroprusside, ML213 (KV7.2-5 channel activator) and NS11021 (BKCa channel activator) on pre-contracted arterial tone (10μM Methoxamine). Changes in vascular remodeling were determined via Sirius red staining of cross sections of 3rd order MAs, in addition to electron microscopy.

Our in vivo investigation revealed a reduction in Blood Pressure within SHRs treated with colchicine when compared to placebo controls across the 4 weeks. Further, colchicine mediated no significant acute changes in blood pressure. Our ex vivo investigations similarly demonstrate an enhanced response to SNP, isoproterenol and ML213 when comparing arteries from Colchicine treated SHRs to placebo controls. Finally, Sirius red and electron microscopy revealed a reduction in media to lumen ratio when comparing the arteries from the same groups.

Collectively indicating that long-term treatment with colchicine has positive outcomes for BP reduction, via enhanced vascular responsiveness to vasodilators coupled with a reduction in detrimental vascular remodeling, implicating colchicine as a novel therapeutic candidate for the treatment of hypertension.

