

Comparison on the effects of resveratrol and resveratrol vehicled in rice oil in models of inflammation in rats

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Resumo

Introduction: Extensive research within the last decade revealed that most chronic disorders such as neurological alterations, diabetes, and autoimmune diseases exhibit deregulation of multiple cell signalling pathways, which are linked to inflammation. Noteworthy, most mono-targeted-based therapies developed during the last two decades for treating inflammatory chronic diseases have proven to be, in some cases, unsafe and ineffective. Resveratrol (trans-3, 5, 4'-trihydroxystilbene; RSV), a component of grapes, berries, peanuts and other traditional medicines, is a polyphenol compound that has been shown to mediate its effects by modulating many different pathways (Kuzhuvelil *et al.*, 2008). This study was aimed at comparing the effects of systemic treatment with resveratrol vehicled in rice oil (RSVO), with those observed for RSV in rat models of inflammation. **Methods:** Male *Wistar* rats (n= 5; 180-200 g) were used. For induction of sub-chronic inflammation, animals received an intradermal injection in one hindpaw (right paw) of CFA (*Mycobacterium tuberculosis*, heat-killed and dried) which was suspended in a 1:1 oil/saline emulsion (in a total volume of 200 µL). As a control, the contralateral paw (left paw) received 200 µL of saline. In this model, the animals were orally treated with RSV or RSVO (100 mg/kg and 10 mg/kg, respectively), 2 h post-CFA injection, and once a day for 3 days. The control groups received the corresponding vehicle solutions at the same intervals of time. The oedema was measured by using a plethysmometer (Ugo Basile) at several time points following CFA injection (2, 4, 6, 8, 24, 48 and 72 h), and it was expressed in mL as the difference between the right and left paws. The chronic arthritis model was induced by CFA injection, as indicated above, and it was assessed daily in a plethysmometer, between days 14 and 21 post-CFA administration. Animals were

treated with RSV or RSVO (100 mg/kg and 10 mg/kg, p.o., respectively), twice a day, for 8 days, starting at the 14th day of CFA injection, until the 21st day. The control groups received the respective vehicles solutions. The occurrence of gastrointestinal lesions was evaluated following the chronic administration of RSV (100 mg/kg), RSVO (10 mg/kg) or the positive control drug indomethacin (3 mg/kg), all administered by oral route, during eight days, twice a day. The intestine (duodenum, jejunum and ileum) was slit open opposite to the attached mesenteric tissue. The organs were washed with saline solution and the mucosal surfaces were macroscopically examined according to an arbitrary scale proposed by Guterres *et al.* (2001). The experimental protocols were approved by the Local Ethics Committee (07/03611, PUCRS). **Results:** The results demonstrated that in the sub-chronic model, for RSV (100 mg/kg, p.o.), the calculated inhibition was $11 \pm 2\%$, until 8 h, and $23 \pm 3\%$, until 3 days of evaluation. Regarding the RSVO (10 mg/kg, p.o.) treatment, the percentages of inhibition were $23 \pm 4\%$ and $21 \pm 2\%$, respectively. Notably, the inhibitions observed for RSVO were significantly higher than those obtained for RSV. In the arthritis model, both formulations were able to significantly reduce the long-term oedema caused by CFA. Again, in these experiments, RSVO (10 mg/kg, p.o.) exhibited a significantly greater inhibition ($29 \pm 4\%$), in comparison to RSV (100 mg/kg, p.o.) ($17 \pm 5\%$). For the gastrointestinal toxicity, the positive control drug indomethacin caused marked alterations of gastrointestinal mucosa, presenting high indexes of lesions. On the other hand, neither RSV nor RSVO elicited any significant change of damage, according to evaluation of ulceration and hemorrhagic scoring, presenting values near to the control groups. **Discussion:** It is tempting to suggest that resveratrol vehicled in rice oil may provide a novel alternative approach as a disease-modifying agent in the progression of inflammatory arthritis. Remarkably, in long-term models of inflammation following CFA injection, RSVO presented an improved gastrointestinal safety. **Financial support:** CNPq, PUCRS.

Referências

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