Resveratrol

Analgesia From Wine to Spine?

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In this issue, Yin and colleagues1 examine the antinociceptive effects of intrathecal resveratrol in a rat model of neuropathic pain. Using a sciatic chronic constriction injury model, the investigators demonstrate a dose-dependent effect of resveratrol on mechanical and thermal hyperalgesia as well as partial reversal of the spinal cord down-regulation of SIRT1, a histone deacetylase whose gene is a putative target of resveratrol.2

Resveratrol, a natural phenol produced by several plants when attacked by fungi or bacteria, has garnered considerable interest given its presence in peanuts, grapes, and wine.3 Resveratrol has been touted with many beneficial effects spanning cardiovascular protection, glycemic control, anticancer and anti-inflammatory effects, and potential life span prolongation.4 As such, it has received significant attention not only in the biomedical literature but also in lay media, especially given its presence in red wine. However, the vast majority of resveratrol studies to date are preclinical with, unfortunately, some contradicting outcomes among the different studies.5,6 And, although there are only limited clinical trials at this stage,1 one study has been halted because of safety concerns.7 Notably, apparent effective doses of resveratrol are orders of magnitude above those found naturally in a cluster of grapes or a glass of wine,8 thus necessitating pharmacological supplementation for clinical efficacy.

The article by Yin and colleagues is a welcome addition to the current literature as it invokes a novel potential beneficial effect of resveratrol as an analgesic. Pain is a primordial, ubiquitous experience that spans many evolutionary stages, and chronic pain involves a number of complex pathways and mechanisms; blocking only one of those is unlikely to result in total abolition of pain. Hence, intrathecal injection of any substance, including resveratrol, would not be expected to abolish chronic pain. Nonetheless, the findings of Yin and colleagues are very encouraging and welcome given current limitations with intrathecal medications9 and the frequent need for intrathecal polyanalgesia.10

The road to clinical intrathecal application of any experimental medication, however, is long and winding and fraught with unexpected and disappointing results.11 For an analgesic agent to be considered for intrathecal drug delivery, its receptor target site(s) must occur predominantly at the spinal level. In addition, significant cerebrospinal fluid concentrations of the drug would not be achieved using systemic administration due to significant first-pass metabolism or poor permeability across the blood-brain barrier. Some pharmacokinetic characteristics of resveratrol appear to favor its consideration for intrathecal application. Resveratrol is a hydrophilic substance12 and as such is a potentially useful intrathecal medication; hydrophilic intrathecal drugs are preferable to hydrophobic agents because the former tend to linger in the cerebrospinal fluid and penetrate deeper into the cord.13 Furthermore, resveratrol appears to undergo extensive first pass-metabolism,14 thus rendering intrathecal delivery an attractive modality. Importantly, the chemical substance under consideration has to be primarily safe for intrathecal delivery and therefore must pass rigorous preclinical safety studies, including experiments using more than 1 large mammalian species, prior to any human trials. Hence, many more pharmacokinetic, safety, and efficacy studies would have to be undertaken before resveratrol is considered for intrathecal clinical trials.

Unfortunately, significant hurdles impede development of newer intrathecal agents. These include not only scientific burdens but also regulatory, economic, and clinical obstacles. It is hoped that introduction of promising agents coupled with renewed interest in intrathecal therapies and improved regulatory paths will lead to development of effective new intrathecal analgesics for the management of refractory chronic pain.
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