Benefits of aging?

Does pain increase or decrease with age, and if so, what causes the change? A factor we considered is that sensitivity to pain could be altered by an age-related loss of neurons involved in regulation of affective/emotional reactivity. For example, aging (and Alzheimer's dementia) involve a progressive loss of neurons that utilize acetylcholine (ACh) to communicate with neurons throughout the brain that regulate emotions. Therefore, understanding some of the changes that occur with advancing years can be approached by examining effects of reduced availability of cerebral ACh on sensitivity to nociceptive stimulation and the emotional reactions pain evokes. First, some background information.

Injection of drugs that mimic ACh (cholinergic agonists) into the cerebrospinal fluid (CSF) surrounding the spinal cord (intrathecal injection) attenuates clinical pain for human patients. This effect indicates that ACh inhibits pain by acting in the spinal cord. However, the brain is not a passive receiver of information from the spinal cord. Interpretation of pain is dependent upon cerebral processing of the emotional impact of noxious stimulation. Therefore, to evaluate the role of cerebral ACh in pain reactivity, we simulated the extreme loss of brain cholinergic neurons that can occur during aging by injecting a selective neurotoxin for cholinergic neurons (192 IgG-saporin) into the lateral ventricles of the brains of rats.

Before and after intracerebroventricular (ICV) injection of 192-saporin, we extensively evaluated the pain sensitivity of the rats. Our method of pain testing allows the animals to choose between standing on a thermally regulated floor (hot or cold) in a dark chamber or moving to a different compartment that is brightly illuminated. The light is mildly aversive/unpleasant, and the floor temperature changes between trials, from non-aversive (32^{o}C) to barely painful heat (44.5^{o} C) or slightly aversive/unpleasant cold (10^{o}C). When the floor temperature is neutral (32^{o}C), the animals choose not to enter the lit compartment, and when the temperature is 44.5^{o}C or 10^{o}C, they cycle back and forth, alternately escaping thermal stimulation and bright light. This method is humane and is not stressful. The animals control the amount of thermal stimulation that is quite tolerable for them and for humans.

Following a substantial loss of cerebral cholinergic neurons from injection of 192 saporin (confirmed by subsequent histological staining of brains), the animals did not have obvious motor deficits or other behavioral abnormalities, but they escaped less from 10^{o}C and 44.5^{o}C. This effect of cholinergic loss in the brain is opposite to a loss of spinal inhibition following intrathecal injection of a spinal cholinergic antagonist.

A review of previous studies and another experiment revealed reasons for reduced pain sensitivity from a loss of cerebral cholinergic neurons. It is known that systemic or intraventricular injections of cholinergic antagonists (ACh blockers) reduce attention and emotional reactivity, including signs of stress, anxiety, fear and depression. The effect of ACh depletion on stress was confirmed by exposing normal rats and the cholinergically deprived animals to loud sound 15 sec. prior to trials

of escape testing. The thermal escape of normal animals, but not the injected animals, was increased by sound stress. Cerebral cholinergic loss following ICV 192-saporin injection substantially reduced stress and the emotional impact of the hot and cold stimuli. Thus, a mellowing of emotional reactivity that is protective against suffering from pain may be attributable to a loss of cerebral cholinergic neurons that progresses to some extent with age for everyone. Also, patients with Alzheimer's disease complain less about pain and receive less pain relieving medication than expected.

Charles J. Vierck[1]***, Robert Yezierski***[1]*and* ***Ronald Wiley***[2]
[1]*University of Florida, FL, USA*
[2]*Vanderbilt University, TN, USA*

Publication

Pain sensitivity following loss of cholinergic basal forebrain (CBF) neurons in the rat.
Vierck CJ, Yezierski RP, Wiley RG.
Neuroscience. 2016 Apr 5