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**“Pain: Mechanisms to Therapy”**

Pain is an extraordinary event. It alerts us to avoid or minimize tissue damage. While the absence of such sensations is catastrophic, the persistence of pain is debilitating. Research has shown that pain consists of three major mechanistic classes: 1) that which arises from acute high intensity stimuli; 2) pain secondary to tissue injury, and 3) that pain which arises after nerve injury. In its simplest expression, pain systems activated by an acute stimulus (a hot coffee cup) represent the activation of small sensory fibers. These fibers project to the spinal cord where they make synaptic contact with a complex of spinal neurons in the dorsal horn that provides an output to specific brain regions. Tissue injury leads to the local release of inflammatory agents that activate and sensitize peripheral sensory terminals. This ongoing afferent input leads to a facilitation of spinal processing so that there is a greater output for any given stimulus. The most perverse mechanisms are those associated with nerve injury. The injured nerve may form an active neuroma. This activity provides aberrant input leading to sensation, as with the phantom pain reported by the amputee. Nerve injury itself leads to a loss of spinal inhibitory neurons, which normally modulate ongoing input. Loss of these neurons leads to an exaggerated response to light touches. These conditions are observed after various nerve injuries arising from chemotherapy, autoimmune reactions or disease.

Control of these pain states has been the focus of much research. The most potent class of drugs for pain control are opioids, such as morphine. Many opiate receptors are present on the spinal terminals of small sensory fibers. Here the receptors block the release of transmitters from the pain fiber. This mechanism has led to invasive therapies employed in severe pain states wherein the patient may receive a chronic spinal catheter connected to an infusion pump that continuously delivers morphine. While morphine may be among the most potent analgesic, the most common is aspirin. These NSAIDs (non-steroidal anti-inflammatory drugs) reverse the hyperalgesic component of tissue injury. Classic work suggested that NSAIDs blocked peripheral inflammation (hence their name). We now know that NSAIDs have a powerful spinal action that blocks the synthesis of prostaglandins responsible for spinal sensitization. After nerve injury there is also a central sensitization that arises because of increased activity that arises from the increased expression of calcium channels within the spinal cord. A component of the venom of a fish killing marine snail blocks one of these channels and such agents can be effective in treating these neuropathic conditions.

There are important *caveats* that make pain difficult to manage. First, many clinical states have multiple components requiring multiple drug targets. Thus, a chronic pain patient may be treated with as many as 3-4 pain medications. Second, genetic components and gender may play a role in certain pain states, such as migraine or fibromyalgia. Even differences in the efficacy of certain analgesics have been reported to be gender related. Finally, while we may have appropriate medications for controlling pain transmission, there is the strong role of higher order function. Imaging the cortical response to a painful stimulus has revealed that areas such as the anterior cingulate cortex and insula, associated with emotionality, may be activated by pain. After hypnotic suggestion, an intense stimulus may be reported to be less painful. This response bias is closely reflected by the associated changes in activity in these cortical structures. The complexities of pain make this a most challenging area of research, but one in which the rewards are great.