relatively smaller than our largest dose when the sensitivity of animals to pentobarbital is taken into account. Because pentobarbital is antinociceptive at the spinal level while suppressing the descending inhibitory system supraspinally, we speculate that increasing doses produce a continuum of effects from disinhibition to suppression of the spinal nociceptive system, resulting in hyperalgesia to analgesia.

The second, and perhaps more intriguing, issue is that pentobarbital appears to differentially affect various pain-related behaviors in the formalin test. Injection of formalin provokes several distinct behaviors, including favoring, licking, and flinching of the injected paw. We used flinching as a measure of pain and demonstrated pentobarbital-induced preemptive analgesia. In contrast, others used the weighted scoring system involving favoring, licking, and flinching, and failed to show an analgesic effect. In this regard, it is noteworthy that intrathecally administered muscimol, a GABA_A agonist, also selectively attenuates formalin-induced flinching while having no effect on the weighted pain score.

In fact, such differential alterations in formalin-evoked pain behaviors are not unique to agents with GABA_A agonist properties. Accumulating evidence suggests that several other classes of agents also cause dissociation among various pain-related behaviors in the formalin test. For example, amphetamine reduces the weighted pain score while leaving flinching unaffected. Naloxone, although not generally accepted as an analgesic, inhibits licking but does not alter and may increase flinching. It is a matter of great controversy which of these behaviors or their combination is the best measure of formalin-induced pain. However, the problem may really lie in the fact that, when dealing with animal models of pain, researchers have predominantly focused on the intensity of pain but have rarely evaluated the quality of pain. Obviously, this approach is too simplistic, because we know pain is a multifactorial phenomenon, at least clinically. That a number of unrelated classes of agents exert such diverse and differential influences on pain behaviors strongly indicate that these drugs may change the quality of pain in a different fashion, resulting in nonuniform alterations in pain behaviors. In our clinical practice, we ask the patient not only “how much does it hurt?” but also “how does it hurt?” Then, why not ask the same questions to animals?

Kaneko M, Hammond DL: GABA acting at GABA_A receptors in the spinal cord limits the second, but not the first phase response to formalin in the rat. Presented on August 20, 1996, at the 8th World Congress on Pain, Vancouver, Canada.

In Reply:—Goto et al. continue an interesting discussion regarding conflicting results among the cited studies. As they reiterate, evidence exists to support the dose dependency of barbiturates on nociceptive behavior. This phenomenon appears to be due to a dose-related progression starting from suppression of descending inhibitory systems (hyperalgesic effect) to suppression of spinal nociceptive mechanisms (analgesic effect). For this reason, differences in behavioral effects of GABAergic anesthetics that have variable pharmacokinetic/pharmacodynamic (PK/PD) profiles must be interpreted with caution. Goto et al. suggest that, in our study, the lack of analgesic effect with pentobarbital may be due to the possibility that the dose used produced roughly equal suppression of both descending inhibitory and spinal nociceptive systems. Although this is a feasible hypothesis, it should be noted that the purpose of our study paradigm is to measure persistent pain during phase 2, which is thought to be an expression of spinal sensitization produced by noxious stimulation during phase 1. The timing and dosing of drugs used in our study was designed to maximize drug effect during phase 1, in an attempt to prevent spinal sensitization while allowing for anesthetic recovery, so as to eliminate or at least minimize residual drug effect during

References


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phase 2. With this in mind, phase 2 pain behavior is interpreted as how effectively the study drug prevented sensitization during phase 1 and less dependent on whether the drug dose was hypnotic or subhypnotic.

Although flinch counting and weighted scores behavioral measurement have both been validated and widely used, Goto et al. emphasize the value of qualitative distinction between different pain behaviors in the rat formalin test. This is an interesting idea, because each of these behaviors may be an expression of diverse subjective sensations and may respond differentially to pharmacologic manipulations.

Given the obvious difficulties in interpreting pharmacologic effects on experimental pain behavior, it is of vital importance that we enhance such behavioral studies with other concomitant measures, such as PK/PD analyses, electrophysiology, molecular biology, and receptor binding assays. Such strategies may provide additional information regarding specific mechanisms of drug action and further aid in clarifying equivocal behavioral findings.

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