Global Year Against Pain in Women

real women, real pain

Sex Differences in Pain – Basic Science Findings

Why is it important to study sex differences in laboratory animals (rats and mice)?

1. Using laboratory animals allows much more powerful experimental techniques to be brought to bear on the problem (e.g., genetic manipulation, electrophysiological recording, experimental drug administration), leading to discovery of underlying mechanisms.
2. Non-human animals are unlikely to have gender-related stereotyped roles, and thus differences seen would likely be "biological" rather than "sociocultural" in origin.

Are laboratory animals of both sexes commonly studied?

NO. A recent survey of papers published in Pain revealed that 79% of all studies employed male subjects only, 8% female subjects only, and only 4% explicitly designed to test for sex differences should they be there. Note that this is in contrast to the situation in humans, where both sexes are now commonly studied.

What findings in this field have achieved consensus?

1. Male rodents are usually more sensitive than females to opioid-mediated analgesia, both from opiate drugs and endogenous release (i.e., stress-induced analgesia); these effects are bigger when using lower-efficacy opiates (e.g., morphine).
2. Steroid hormones clearly and often robustly affect pain sensitivity in rodents (estrogen, progesterone, and testosterone), although the direction of effect is variable.
3. Sex differences in pain/analgesia are likely to be found within the descending pain modulatory pathway (periaqueductal gray→rostroventral medulla→spinal cord).
4. There appears to be sex-specific analgesic mechanisms, involving at least partially divergent genetic and neurochemical factors. These may relate to the phenomenon of pregnancy-induced analgesia.
5. Sex differences interact importantly with genetic background.

What findings are still controversial?

1. Whether male and female rodents differ significantly in their sensitivity to noxious stimuli. The answer appears to depend importantly on the test used and the genetic background of the tested population.
2. Whether pain/analgesic sensitivity differs across the estrous cycle (the rodent equivalent of menstrual cycle). Any number of studies have reported such differences, but the directions of effect are contradictory.

What genes/proteins have been implicated in sex differences in pain/analgesia?

1. Estrogen Receptor
2. Mu- / Kappa- / Delta-Opioid (MOR, KOR, DOR) Receptors
3. GABA-A Receptors
4. N-methyl-D-aspartate (NMDA) Receptor
5. Melanocortin-1 Receptor (MC1R)
6. Orphanin FQ/Nociceptin (OFQ/N) Receptor
7. Protein Kinase A/C
8. G-protein-coupled Inwardly Rectifying Potassium Channel (GIRK2)
9. Acid-Sensing Ion Channel (ASIC)
10. Alpha2-Adrenergic Receptor

What exciting new developments have occurred recently?

1. Interaction of sex and social context in mice.
2. Sex differences might be produced directly by sex chromosome (X&Y) genes, rather than by gonadal hormones.
3. There are sex differences in itch as well as pain.
4. Sex differences in pain/analgesia are already present on the day of birth.
5. There are sex differences in morphine tolerance and dependence.
6. There are sex differences in mechanisms of inflammation.

What differences are there between sex differences in rodents versus humans?

1. It is not clear that opioids are more effective in men compared to women. There are reports supporting both points of view. The animal literature, by contrast, strongly supports greater opioid efficacy in males.
2. Differences between women and different species of rodents in timing and hormonal variations during their fetal development, their puberty, their ovarian cycle and their progression through reproductive senescence are important considerations in translating research findings between female rodents and women.