CASE STUDY: Commonly Prescribed Anti-Depressants

Depression is becoming an ever-increasing problem in our society with an expanding incidence of depression occurring in the younger generation (need ref for this). However, there have also been tremendous advances in several drugs that are used to treat clinical depression, and their widespread use makes the importance of studies looking at their effectiveness and long-term benefits all the more crucial.

The neurotransmitter serotonin is released from the presynaptic terminals of axons and is thought to control many physiological processes such as mood, sleep, anger, aggression and appetite. The action of serotonin is modulated by down-regulation when it undergoes re-uptake into the pre-synaptic dendrites of adjacent neurons by binding to specific serotonin receptors. The drugs prozac and paxil act at the site of re-uptake by inhibiting the serotonin receptors with little or no activity against other tested receptors, however given its effects on a number of other physiological processes suggest that these drugs may have some non-target activities.

Pharmacology is a difficult area of study because it is difficult at best to understand the complex metabolism and off-target effects elicited by the treatment with various drugs. Before approval for use in humans, all drugs undergo extensive animal testing, usually in mice; however the ability to rapidly look at alternative drug action and selection of different mutants that may be more or less sensitive to the drug can be very slow. Scientists therefore often turn to simpler model organisms, such as C. elegans or D. melanogaster that have short life-spans and have a very well-defined neurological system. The following questions are based on a series of experiments carried out in C. elegans looking at the action of prozac.

Questions:

1. In C. elegans, the MOD-5 gene encodes the only version of the serotonin reuptake transporter in this organism. Mutations in the MOD-5 gene are hypersensitive to exogenous treatment with serotonin and have an elevated response to a normal behavioral response to serotonin exposure (slow response to food). These effects could be potentiated by treatment of the animals with prozac, a serotonin reuptake inhibitor. Strikingly, treatment of the worms with high levels of prozac also caused a defect in which the animals contracted their noses, a response that was not eliminated in animals that had a mutation in the MOD-5 gene. How can you interpret this result for what happens in worms?

Answer: These results imply that prozac induces multiple effects in C. elegans. Some of these effects are mediated by the serotonin reuptake transporter MOD-5, while other effects must be mediated by action on other proteins.
2. What do these results imply for the use of prozac in humans?

Answer: These results imply that drugs such as prozac may be exhibiting part of their physiological response by activities distinct from the proposed primary site of action.

3. Can you think of a way that scientists could use a genetic organism such as C. elegans to identify these other targets of prozac?

Answer: Because the animals exhibit an easily recorded phenotype (retraction of their noses) it should be possible to look for worm mutations that eliminate this phenotype upon exposure to prozac. The corresponding genes could be cloned to identify genes important in this process.

Where can I learn more?