Social Amoeba Sheds Light On Communication In Human Brain

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Sherry Seethaler

Biologists at UCSD have discovered that the popular sedative Valium has similar effects on the social amoeba *Dictyostelium discoideum* as it does in humans. Their surprising finding that Valium, as well as a "natural Valium" molecule found in human brains, causes the social amoeba to enter a dormant or "sleep" phase, may provide new insights into how cells in higher organisms, including humans, communicate with each other.

The study, published this week in the early on-line edition of Proceedings of the *National Academy of Sciences* and to appear in the print edition of *PNAS* May 24th, describes the discovery of a short protein, or peptide, known as SDF-2, that neighboring cells of *Dictyostelium* use to synchronize the formation of spores-the dormant phase of the organism. The researchers were surprised to find that SDF-2 is similar to a "natural Valium" peptide-called DBI-that is found in human brains. Both DBI and Valium cause *Dictyostelium* to form spores.

"It was amusing to discover that Valium puts *Dictyostelium* to sleep and Valium puts humans to sleep," said William Loomis, a professor of biology at UCSD, who led the study. "But more significantly, our findings confirm that *Dictyostelium* is an excellent experimental system for studying aspects of communication between cells that are not easily amenable to study in complex multicellular organisms."

Loomis and Christophe Anjard, an assistant project scientist in Loomis' laboratory, and first author on the paper, also speculate that spore formation in *Dictyostelium* might provide a rapid way to screen for new drugs that mimic the anti-anxiety effects of Valium in humans.

"Both DBI and Valium induce spore formation in *Dictyostelium*, and flumazenil, a drug that inhibits the effects of Valium in humans, inhibits spore formation," explained Anjard. "Using *Dictyostelium* to screen for drugs that function like Valium would be very cheap and could identify potential drugs within hours."

Individual cells of *Dictyostelium* usually live independently, but when food is scarce the cells form spores. During spore formation, up to one hundred thousand cells cooperate with each other to form a stalk that resembles a golf tee. The formation of spores must be carefully regulated because prior to turning into spores, cells need to climb to the top of the stalk, where they can be more easily dispersed by the wind.

The researchers inferred that cells at the base of the stalk cut up a longer protein to produce the SDF-2 peptide. They said that there is much to be learned about how DBI is made from its longer protein precursor, and what role that longer protein may play in human cells.

"Despite the interest in the role of DBI in the human brain, no one has really looked to see how the DBI peptide is processed from its precursor protein," explained Anjard. "Also, the precursor to SDF-2 plays a 'housekeeping' role in *Dictyostelium* cells, shuttling fats between membranes. It would be interesting to find out if the precursor to DBI plays a similar role in human cells. We hope that our findings will reactivate research in this area."

Loomis and colleagues are currently working to determine the crystal structure of the receptor for the SDF-2 peptide. The researchers say that its structure should be easier to obtain than the structure of the receptor for

DBI-also known as the GABA receptor-which has so far been elusive. The amino acid sequence of the two receptors is different, but because the receptor for SDF-2 responds to DBI and Valium, its crystal structure could provide new information about the functioning of the GABA receptor.

"The trick in deciphering complex signals between cells is to find an experimental system that is complex enough to have the signals that are interesting, but simple enough to permit you to test your hypothesis," said Loomis. "Once you have an idea of how things work, it is easier to go back and see if they work the same way in a more complex system."

"Most processes cells use to communicate with each other have been around a long time in evolutionary terms," added Anjard. "For example, we might have thought that DBI and its receptor were unique to higher animals, but now we have discovered that this signaling system is also being used by a single-celled organism."

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Media Contact: Sherry Seethaler (858) 534-4656 Comment: William Loomis (858) 534-2543