feeders[10,11]. What makes *Hymenochirus* so unusual is not just its size or feeding mode, but also that it is phylogenetically nested in a group of obligate suspension feeders[3,12] and has independently evolved suction-feeding mechanics that are highly convergent with those of teleosts.

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Purinergic receptors

An ATP-gated ion channel at the cell nucleus

Transcriptional activity inside the nucleus of eukaryotic cells is regulated by ions such as calcium that need to be transported across the nuclear membrane. Here we show that an ion channel spanning the nuclear envelope between the cytoplasm and the nucleus could be regulated by an ATP-binding receptor of the $P2X_7$ subtype. Activation of this nuclear $P2X_7$ receptor by ATP in the cytoplasm may be a mechanism by which cellular activity can be coupled to changes in gene expression.

$P2X_7$ receptors are members of a family of ATP-binding receptors that are permeable to calcium. Originally thought to be absent from neurons[1], the $P2X_7$-receptor subunit $P2X_7R$ has been shown to be targeted to excitatory but not inhibitory terminals, and yet it is absent from plasma membranes of the cell body[2,3].

To determine whether inhibitory neurons also express the receptor, we used *in situ* hybridization of the rat hippocampus to detect messenger RNA encoding $P2X_7R$. A positive signal was seen in the cytoplasm of all neurons in the cell-body layer[3], 90% of which are excitatory cells[4]. In contrast to the localization of the $P2X_7R$ protein to the terminals of only excitatory neurons, however, $P2X_7R$ mRNA was also present in cells containing immunoreactivity for the potassium-channel subunit Kv3.1b, which identifies a subset of inhibitory neurons in the hippocampus[5] (Fig. 1a, b).

The mismatch between the expression of $P2X_7R$ mRNA and its protein in inhibitory neurons was explained when we used different antisera to stain the intracellular (specific to amino-acid residues 576–595; 1:1,000 dilution; refs 2, 6) and extracellular (specific to amino acids 60–323; 1:100 dilution; ref. 6) portions of $P2X_7R$ and found staining adjacent to the nuclear envelope in 100% of hippocampal neurons (Fig. 1c, d).

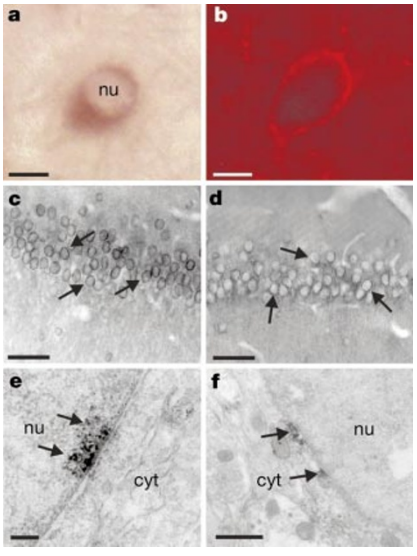

Figure 1 An ATP-gated ion channel spans the nuclear envelope. **a,** Messenger RNA encoding $P2X_7R$ (visualized with alkaline phosphatase[2]) is present in the cytoplasm of all neurons in the hippocampus, and is shown in one neuron (nu, nucleus) adjacent to the cell-body layer; **b,** this neuron is identified as inhibitory by the presence of predominantly membrane-bound red Kv3.1b immunofluorescence (antibody against the K^+-channel subunit Kv3.1b from Alomone Labs). **c, d,** Localization by light microscopy of $P2X_7R$ protein: 'intracellular' (**c**) and 'extracellular' (**d**) epitopes are seen adjacent to the nuclear membrane (arrows) in all neurons in the cell-body layer. **e, f,** Immuno-electron microscopy of $P2X_7R$, seen here spanning the nuclear envelope, with **e**, its 'intracellular' portion adjacent to the nuclear side of the nuclear envelope (arrows), and **f**, its 'extracellular' portion facing the cytoplasm (cyt; arrows). Scale bars: **a**, **b**, 5 μm; **c**, **d**, 50 μm; **e**, **f**, 0.5 μm.

The protein must span the nuclear envelope because the antisera against the two different epitopes labelled the cytoplasmic and inner surfaces of the nuclear membrane, respectively, with the ATP-binding site being in the 'extracellular' portion facing the cytoplasm (Fig. 1e, f). This finding still leaves unanswered the question of how $P2X_7R$ is transported selectively to the presynaptic terminal in only excitatory neurons but to the nuclear envelope in all neurons.

Insertion of $P2X_7R$ into the nuclear envelope is consistent with patch-clamp studies on nuclei showing that ATP binding maintains the open state of non-selective cation channels[7] as well as inducing a macroscopic current[8]. The properties of $P2X_7Rs$ correlate with these nuclear channels as they exhibit little or no desensitization[9], they are activated by ATP (the 50% effective concentration is about 100 μM (ref. 9), which is well within the 5–10-mM range of cytoplasmic ATP), and they form a large pore upon prolonged activation[9] (which may correspond to the ATP-induced macroscopic current in the nuclear membrane[8] and the increase in envelope permeability induced by ATP binding[7]).

Moreover, the ATP-gated nuclear channels[7,8] and the $P2X_7R$[9] are both permeable to Ca^{2+} ions, and changes in nuclear Ca^{2+} concentration are linked to changes in the transcription of several genes implicated in neuronal plasticity (principally by regulating the activity of the transcriptional co-activator protein CBP)[10]. The presence of $P2X_7R$ in the nuclear envelope of phenotypically heterogeneous neurons and of ATP-gated channels in nuclei of diverse cell types (such as *Xenopus* oocytes and mouse liver cells) therefore has wide implications as it provides a means of regulating nuclear Ca^{2+} concentration in response to cytoplasmic activity.

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