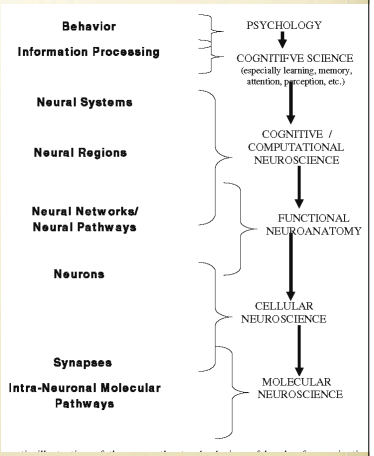
Reduction II: Ruthless REductionism

The Multiple Bridge View

- Bickle sets up as an alternative to his ruthless reductionism a perspective in which reduction must proceed step-by-step from each level to the one immediately below it
- Defenders of the theory-reduction view often focus on reduction to some basic level, but this is accomplished via a sequence of step-wise reductions
  - An important components of each step in the reduction is the role of boundary conditions which limit the context in which the lower-level laws give rise to the higher-level regularities
  - What happens to these on the ruthless account?

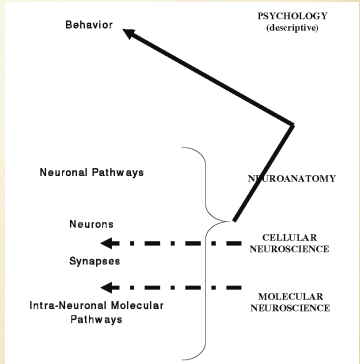


Skipping the Intermediaries

- Bickle's ruthless reductionism cuts right through the intermediary levels to that of cell and molecular processes
- Strategy: Intervene at the molecular or cell level, detect effects at the behavioral level
  - "intervene causally at the level of cellular activity or molecular pathways within specific neurons (e.g., via genetically engineered mutant animals);
  - "then track the effects of these interventions under controlled experimental conditions using behavioral protocols well accepted within experimental psychology."
- "One only claims a successful explanation, a successful search for a cellular or molecular mechanism, or a successful reduction, of a psychological kind when one successfully intervenes at the lower level and then measures a statistically significant behavioral difference."

Skipping the Intermediaries

- "When this strategy is successful, the cellular or molecular events in specific neurons into which experimenters have intervened, in conjunction with the neuronal circuits in which the affected neurons are embedded, leading ultimately to the neuromuscular junctions bridging nervous and muscle tissue, directly explain the behavioral data."



What Role for Higher Levels in the Brain?

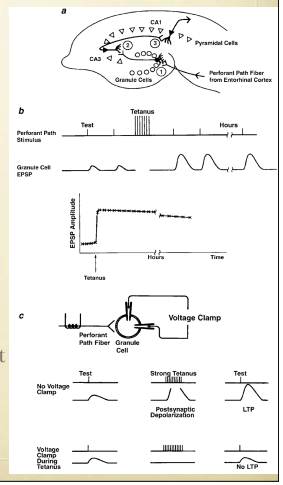
- Servants of the cell and molecular level research. Useful to answer questions such as:
  - What are good experimental protocols for tracking behavioral outcomes for the psychological phenomenon we seek the cellular and molecular mechanisms of?
  - Where shall we begin inserting our cellular and molecular interventions? (The possibility space in both brains and intra-neuron molecular pathways is enormous!)
  - What kinds of neural activities seem to be involved? (Spiking frequency? Spiking pattern? Field potentials? Synaptic plasticity? This list only scratches the surface of possibilities, and each entry involves quite different molecular mechanisms.)
- These questions are (only) heuristic: they serve "the search for underlying cellular and ultimately molecular mechanisms."

Contrast with the Theory Reduction Account

- On the theory reduction account, the goal was to recover the higher-level theory from the lower-level one
  - "On successful 'intervene molecularly and track behaviorally' reductions, explanations of behavior no longer appeal to features of higher levels (besides those of the functional neuroanatomy of the organism under investigation).
- The theory reduction view appealed to laws, generalizations, or model-theoretic components
  - But ruthless reductionism does not
    - Neither does cell and molecular neuroscience
- Theory reduction accounts aim at reducing to more general theories
  - Ruthless reduction only appeals to regularities in very restricted contextts

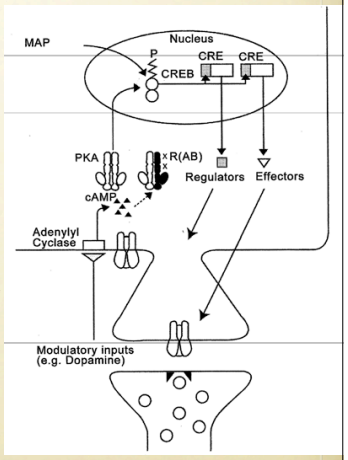
Case I: LTP

- Memory consolidation: When acquiring new information, organisms can retain it briefly in short-term/working memory, but for it to be maintained for longer periods it must be *consolidated* into long-term memory
- The discovery of long-term potentiation in cells in the hippocampus provided a candidate mechanism
  - Electric stimulation of neurons results in increase lasting for hours/days/weeks in excitatory post-synaptic potentials (EPSPs) to inputs on axons that synapse there
  - Ongoing theta (5-7 Hz) oscillations linked to LTP
    - They involve inputs on interneurons that project to the same synapse as the excitatory projection representing the stimulus and together provide the equivalent of the tetanus



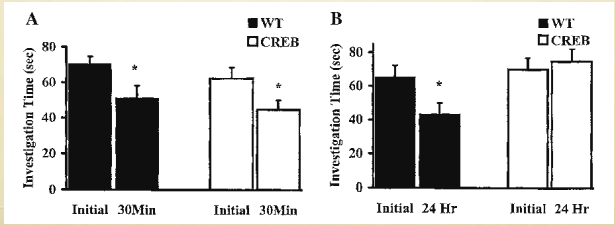
What Explains LTP?

- LTP itself is a cellular phenomenon involving changes in synapses
- Molecular processes in LTP have been identified
  - Dopamine from the interneurons primes Adenylyl Cyclase, which catalyzes reaction from ATP to cAMP
  - cAMP binds to regulatory subunits of protein kinase A (PKA)
  - PKA turns off inhibition of phosophorylated calcium-calmodulin kinase II (CaMKII), allowing it both to bind to AMPA receptors to move them to synapse and to bind with cyclic AMP response element binding protein (CREB), which turns on gene expression needed to build new synapses



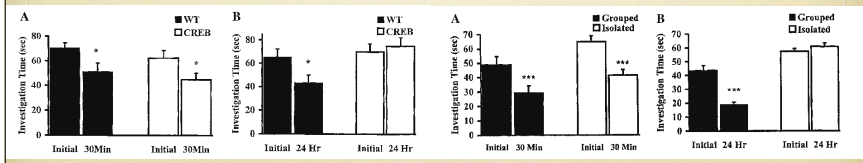
Case 2: Linking LTP to Memory

- Silva and colleagues have intervened in part of the LTP mechanism
  - Creating knock outs of two isoforms of CREB by inserting a targeting vector into embryonic mouse stem cells which are transferred into blastocytes where they disrupt CREBαδ expression
- The interventions produce memory deficits
  - Long-term amnesia for social recognition without affecting initial learning or sort-term recognition memory involving associating a context with a shock
  - Recognizing a previous encountered individual after 24 hours--measured in reduction of time investigating that individual compared to a novel individual



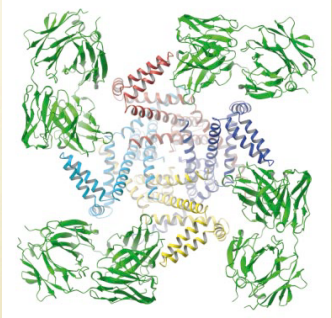
Comparison with Behaviorally-induced Deficit

- Rearing mice in socially isolated environments for three weeks prior to experiment produced the same result
  - "This raises the intriguing possibility that CREB α and δ isoform availability in various neurons is a molecular mechanism through which a cause as "high level" and "external" as a mammal's environmental interactions with conspecifics affects a central kind of cognition and behavior (social recognition memory).
- Note: the fact that two interventions have comparable effects does not show that they are produced in the same way



How Far Down Should the Reductionist Go?

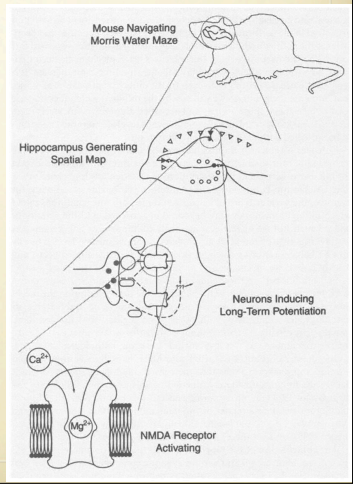
- As far down as researchers can intervene directly and produce changes in the phenomenon to be explained
- We are already in the early days of "intervene biophysically and track behaviorally"
  - Tools such as nuclear magnetic resonance imaging is making it possible to image the structure of proteins
  - Proteins have "active sites" at which they mind substrates and catalyze reactions
  - The overall structure of proteins is continuously changing, and this often affects the ability of molecules to bind to the active sites
  - In many areas of biology, one can identify structural changes that affect the phenomenon of interest



Voltage-dependent potassium ion (K^+) channel

Ruthless Reduction: What is the Goal?

- What is the goal of focusing one's efforts on intervening at the cell or molecular level?
  - The things that make a difference to the phenomenon seem to be explanatory
    - The CREB deficient mice failed in social recognition tasks *because* they failed to generate CREB αδ isoforms
  - The processes identified provide a potential target for intervention
- Does ruthless reduction involve a commitment to replacement or elimination?


Mouse Navigating
Morris Water Maze
Hippocampus Generating
Spatial Map
Neurons Inducing
Long-Term Potentiation
Ca^{2+}
Mg^{2+}
NMDA Receptor
Activating