the resemblance of the structures of the ATD/LBD and TMD with the amino-terminal domain of mGluRs and potassium channels (see Chapter 13), respectively. Functional receptors are comprised of four subunits assembled around the ion channel lined by M3 helices from each subunit. All NMDA receptors are heteromeric assemblies as GluN1 together with either GluN2 and/or GluN3 subunits whereas AMPA and kainic acid receptors can either be homo- or heteromeric assemblies.

High-resolution 3D structures of the isolated LBD of the majority of ionotropic glutamate receptor subunits and of full-length GluA2 and GluN1/2B receptors have been determined in the absence of ligands and with full and partial agonists, antagonists, and/or allosteric modulators. Overall, these studies have shown that, like the mGluR receptors, activation is initiated by closure of the LBD around the ligand which leads to an outward pull of the M3 gating helices causing an opening of the channel pore (Figure 12.7). The plentitude of LBD structures has also provided a compelling insight into ligand–receptor interactions, molecular mechanisms of selectivity and efficacy. Such information is very valuable in the design of glutamate receptor subtype selective compounds as will be discussed in further detail in Chapter 15.

12.2.2.3 Purinergic P2X Receptor Family

ATP is primarily considered as an intracellular energy storage molecule, but also acts as an intercellular signaling molecule activating a group of P2Y GPCRs and seven $P2X_{1–7}$ ligand-gated ion-channels. Recent 3D structures of a full-length $P2X_4$ receptor has shown that the receptor consist of three homo- or heteromeric subunits which form a pore in the cell membrane (Figure 12.8). The orthosteric binding site is located in the three subunit interfaces in the extracellular domain. Comparison of the inactive apo (without ligand) and active ATP-bound structures have revealed that agonist binding leads to conformational changes in the extracellular domains which is relayed to the transmembrane domains causing opening of the nonselective cation channel (see Figure 12.8 for details).

12.2.3 Tyrosine Kinase Receptors

As illustrated in Figures 12.9 and 12.10, the tyrosine kinase receptors have a large extracellular agonist binding domain, one transmembrane segment, and an intracellular domain. The receptors can be divided into two groups: those that contain the tyrosine kinase as an integral part of the intracellular domain and those that are associated with a Janus kinase (JAK). Examples of the former group are the insulin receptor family and the epidermal growth factor (EGF) receptor family and examples of the latter are the cytokine receptor family such as the erythropoietin (EPO) receptor and the thrombopoietin (TPO) receptor. However, both groups share the same overall mechanism of activation: Upon agonist binding, two intracellular kinases are brought together which will initiate autophosphorylation of tyrosine residues of the intracellular tyrosine kinase domain (Figure 12.9). This will attract other proteins (e.g., Shc/Grb2/SOS and STAT for the two receptor groups, respectively), which are also phosphorylated and this will initiate protein cascades and ultimately lead to regulation of transcriptional factors (e.g., Elk-1, Figure 12.9) and thus regulation of genes involved in, e.g., cell proliferation and differentiation. As described for the GPCRs, all the proteins in the intracellular activation cascades are heterogeneous leading to individual responses (i.e., regulation of different subset of genes) in individual cell types.

Albeit the tyrosine kinase receptors share the overall activation mechanism, the family has turned out to be rather heterogeneous with respect to the structure and ligand–receptor interaction. Some of the receptors exist as monomers (e.g., the EGF receptor family) in the absence of agonist whereas others exist as covalently linked dimers (e.g., the insulin receptor family) or noncovalently linked dimers (e.g., the EPO receptor). In case of the monomers, agonist binding to either one or both subunits will bring the two receptor subunits together, and thereby initiate the autophosphorylation. In case of the preformed inactive dimers, agonist binding will cause a conformational change in the receptor which brings the two intracellular kinases together and thus initiate the