ANSWERS Cell signaling part 2

1A) It would probably cause receptor activation, because it can bind two receptor monomers, causing their dimerization and subsequent trans-phosphorylation (mimicking the effect of the natural ligand of that receptor).
1B) The kinase domain of a RTK is present on the intracellular side of the receptor. Hence, nothing would happen, because an antibody cannot enter cells, being much two large and hydrophilic.

2)

A. No. An extracellular molecule will bind a GPCR. B. Yes. C. Yes.

D. No. cAMP is produced from ATP.
E. No. cAMP activates protein kinase A.
F. No. cAMP can be transported to other cells via GAP junctions. G. Yes.

3)

A. No. RAS is a small GTPase. It does activate RAF.
B. No. On the contrary, EGF-R is a proto-oncogene. Its mutation in cancer cells leads to overactive EGF-R kinase activity.

4) The mutant G protein would be constantly active. Each time the α subunit hydrolyzed GTP to GDP, the GDP would dissociate spontaneously, allowing GTP to bind and reactivate the α subunit, especially because the intracellular concentration of GTP is higher than that of GDP. Normally, GDP is tightly bound by the α subunit, which keeps the G protein in its inactive state until interaction with an appropriate activated GPCR stimulates the release of GDP.

5) This treatment will not work. Indeed, the KRAS mutant protein is constitutively active in tumor cells, independently from upstream signaling events such as RTK dimerization. Only drugs disrupting KRAS directly, or downstream events in this signaling pathway would be candidate drugs against KRAS mutant pancreatic cancer.

6) Changes in ion concentration are key in order to be able to utilize them for signaling purposes. To increase Ca^{++} concentration by 10x, it is sufficient to let relatively small quantities of Ca^{++} in (the starting concentration is only 10^{-7} M). In contrast, to increase the Na^{+} concentration by 10x, many more (10^{4} more) Na^{+} ions need to enter. Changes in the micromolar range are more easily achieved than changes in the millimolar range.

7)

A) Effector protein will be inactive, and the cellular response will not happen 2) the effector protein will be constitutively active and the cellular response will happen whether the RTK is activated or not.
B) MAP kinase Kinase, MAP Kinase Kinase Kinase and RAS
C) Potentially PI3 Kinase signaling and PLCy signaling are activated. In the RTK the docking complex for the SH2 domain containing proteins have to be present. i.e. tyrosine amino acids that can be phosphorylated and a.a. that mediate SH2 binding.

8)
A) False. It is the substrates for PKA, not PKA itself, that differ in different cell types.

B) True. The activity of a population of protein molecules whose activity is regulated by phosphorylation depends on the percentage of the molecules that are phosphorylated, which in turn depends on the relative rates of phosphate addition and removal.

C) True. Intracellular signaling pathways that involve enzymes or ion channels can significantly amplify a signal. Once activated, a protein kinase, for example, can phosphorylate hundreds of its target proteins. Similarly, activation of an ion channel can raise the cytosolic concentration of a critical ion by many folds.

9) The "cyclic" in cyclic AMP refers to the ring of atoms formed by the phosphorus atom, its two oxygen atoms, and the carbons at the 3′, 4′, and 5′ positions of the ribose sugar (Figure 15–29). he ball-and-stick representations above and below the chemical formula give a more realistic representation of the chemical structure. he six-member phosphodiester ring is fused to the five-member ribose ring, forming a fairly planar structure that resembles the adenine ring in size and shape. In the more common representation (center), the phosphodiester ring looks very strained, but in reality, it's not.

10) When CaM-kinase II is exposed to Ca2+/calmodulin, it becomes an active protein kinase and phosphorylates adjacent copies of itself in its multi- copy complex. In its phosphorylated state, CaM-kinase II remains active even in the absence of Ca2+, thereby prolonging the duration of the kinase activity beyond that of the initial activating Ca2+ signal. Its self-phosphorylation allows it to "remember" its exposure to Ca2+/calmodulin. It finally "forgets" when a protein phosphatase removes the phosphate, shutting of its activity.

11) You would expect to see several differences. (1) You would expect a high background of Ras activity in the absence of an extracellular signal because Ras cannot be turned of efficiently. Since Ras activity depends on the balance between its binding to GTP and its GAP-enhanced hydrolysis of GTP, the balance would be somewhat more in favor of the GTP-bound (active) form than normal. (2) As some Ras molecules will already be in their GTP-bound form, Ras activity in response to an extra- cellular signal would be greater than normal but would saturate when all Ras molecules were converted to the GTP-bound form. (3) he response to a signal would be less rapid because the signal-dependent increase in GTP-bound Ras would occur over an elevated background of preexisting GTP-bound Ras. (4) the response would be expected to be more prolonged than normal and to persist for a while even after the extracellular signal was removed because of the slower rate of conversion of GTP- bound Ras to its inactive GDP-bound form.

12) The very steep response curve for activation of MAPK converts it into a molecular switch. Thus, MAPK goes from inactive to active over a very narrow range of input stimulus. his kind of behavior keeps the cascade turned of below a threshold concentration of the input signal, yet delivers a maximum response once that threshold is exceeded.