## QUESTION 1 *(Principle: The Graded Dose-Response Curve)*

A 34-year old man is brought to the emergency room in a disheveled and unresponsive state. His vital signs reveal a heart rate of 26 bpm and he is apneic. He has no palpable blood pressure, but has a palpable slow pulse in his femoral artery. Fresh needle track marks, consistent with recent injections, are present in his left antecubital fossa (elbow pit). He is suspected to be a victim of the epidemic of superpotent heroin, "China White". Heroin overdose is typically treated by I.V. administration of naloxone (a drug that binds to the same site on the mu-opioid receptors as heroin, but without the narcotic effects of heroin). Despite oral intubation, mechanical ventilation, advanced cardiac life support measures, and large intravenous doses of naloxone, the patient died.

Part 1 *(Teaching Point: Graded Dose Response Curves for Various Opiate Receptor Agonists)*

China white is the street name for 3-methyl-fentanyl, a short-acting synthetic opioid agonist estimated to have 10,000 times the potency of **heroin** at mu-opioid receptors. Pharmaceutical fentanyl has a potency of 100 times that of **heroin**, while the commonly used opioid analgesic morphine is approximately 5 times less potent than **heroin**. All four drugs are equally efficacious with respect to the effects produced by their activation of mμ opioid receptors.

If the potency of **heroin** at mu-opioid receptors is 10 mg/kg, using the axes below, draw semi-logarithmic dose-response curves to show the expected relative relationships between heroin, fentanyl, morphine and China White (3-methyl fentanyl), indicate their respective ED50's and show in the figure how these are values are determined.
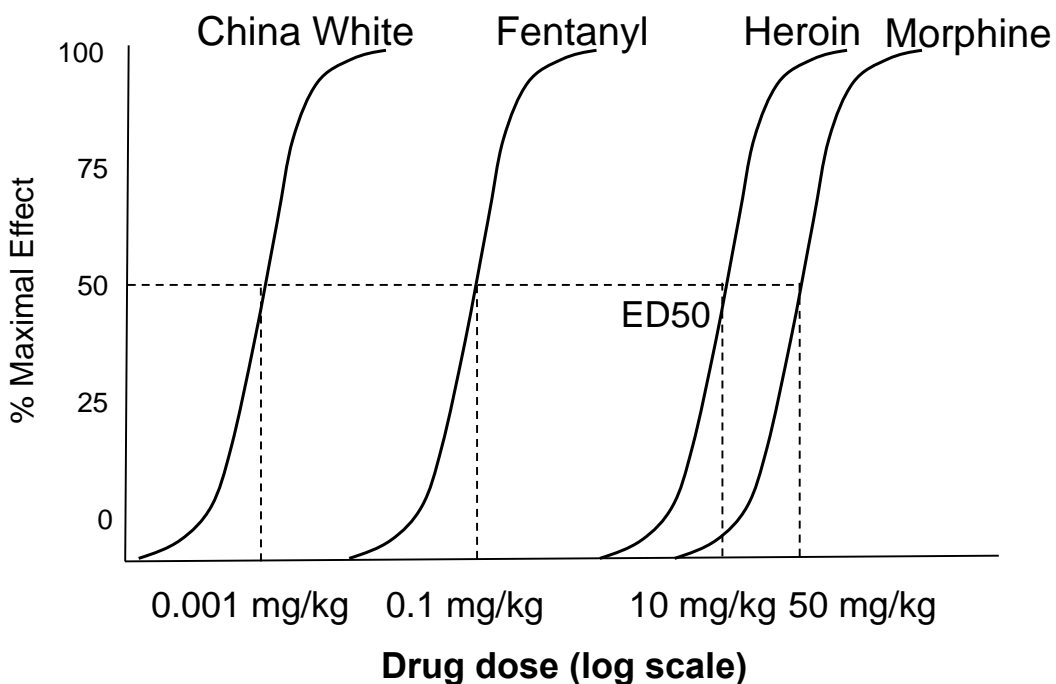
Part 2 *(Teaching Point: Different Types of Pharmacological Antagonism)*

Heroin users have sought out the use of China White (3-methyl fentanyl) to experience the intense rush and thrill of taking a more potent drug, despite its greater life-threatening effects. Indeed, many unsuspecting users suffered cardiorespiratory arrest within minutes after a single injection of China White. Those who survived to receive medical attention required large doses of naloxone for complete reversal of the symptoms. However, in many cases, patients experienced resedation shortly after naloxone administration and required multiple repeated doses of naloxone to ultimately alleviate the effects of 3-methyl fentanyl (China White).

(i)   Given this scenario, naloxone would be <u>best</u> characterized as which one of the following drugs listed in A-D below? Please provide an explanation to support your answer and explain why you ruled out the other choices.

A. A reversible competitive full agonist

B. A reversible competitive antagonist

C. An irreversible noncompetitive antagonist

D. A reversible competitive partial agonist

FACILITATORS ANSWER

The CORRECT answer is B*. **In the presence of a reversible competitive antagonist, the agonist dose response curve will be shifted toward the right (both in systems with or without spare receptors). This is because the antagonist and agonist are competing for the same population of receptors and in the presence of the antagonist, it will require a higher concentration of agonist to occupy any given fraction of receptors than was required in the absence of antagonist. This is referred to as a "surmountable" antagonism, as the effects of the antagonist can be overcome by higher concentrations of agonist, and the original Emax can be achieved by the agonist, albeit, at higher concentrations than in the absence of the antagonist. <u>Consequently, there will be a shift to the right in the agonist DR curve with an increase in the ED50 value but no change in the magnitude of Emax.</u>***

Choice A is INCORRECT: *A reversible full agonist is not the correct answer as this would also stimulate the opiate receptor to the same extent as heroin and not reverse the adverse affects attributed to activation of this receptor.*

Choice C is INCORRECT: An irreversible noncompetitive antagonist is not the correct answer as <u>a single administration of an appropriate dose could completely block opiate receptors and reverse the adverse affects of the opiates</u>. **This** *would not need to be administered repeatedly (as indicated in the scenario) to completely reverse the effects of China White*.

Choice D is INCORRECT: A reversible competitive partial agonist is not the correct answer as administration of a partial agonist may attenuate the effects of the full agonist, China White (3-methyl fentanyl), but it would not completely reverse the opiate effects since complete receptor occupation by the

partial agonist will result in some level of activation of opiate receptors and a response up to the Emax of the respective partial agonist, which by definition is less than the Emax of the full agonist.

   (ii)   Please provide semi-logarathmic dose-response plots in the axes below to illustrate what effect naloxone would be expected to have on the ED50 and Emax of a heroin dose curve.
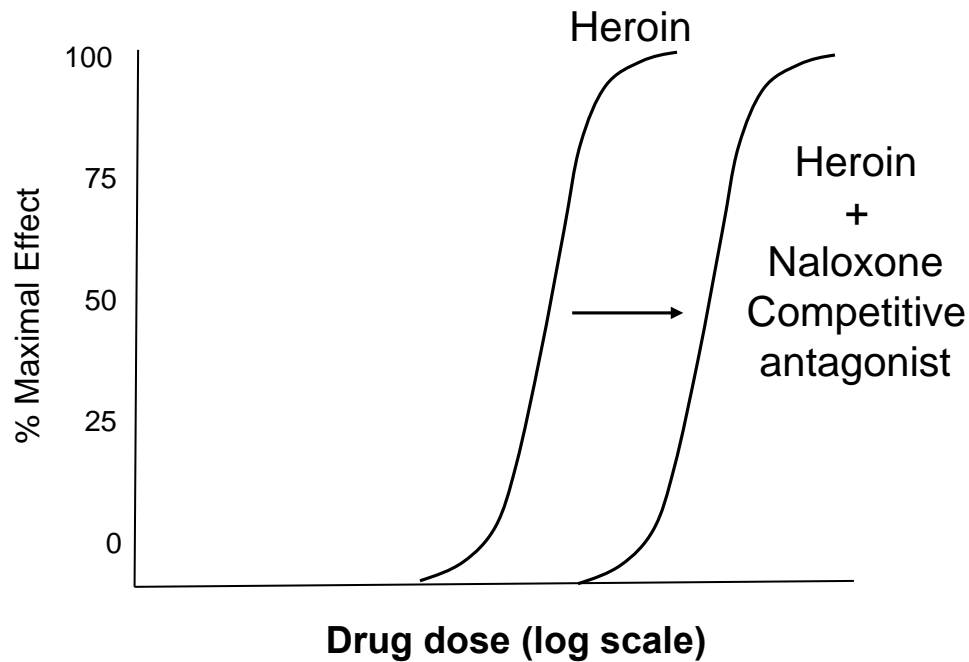
FACILITATORS ANSWER

Reversible competitive antagonists will shift the DR curve of agonists to the right (i.e. increase the EC50) since, in the presence of the antagonist, higher agonist concentrations are required to achieve the same degree of receptor occupation than were required in the absence of the antagonist. At some concentration, the original Emax can still be achieved, so there is no change in the Emax for the agonist, although this requires higher agonist concentrations in the presence of the antagonist. Since higher concentrations of agonist can overcome the effects of the antagonist, this type of pharmacological antagonism (i.e. competitive) is referred to as a surmountable type of antagonism.

Part 3 *(Teaching Point: Understanding the ED50 of a Quantal Dose Response Curve)*
Heroin is usually sold in bags containing a dose of 25-mg and it is common for addicts to use 3 bags of heroin to achieve the "desired high" from this drug. Unsuspecting users of China White (3-methyl fentanyl), who might have achieved a desired "high" with three bags of heroin, died after injecting only one 25 mg bag of 3-methyl fentanyl.

1. **If 50% of China White users died after injecting one bag of the drug, which one of the following statements is most correct** ?

    A. Only 50 % of heroin users are more sensitive to the effects 3-methyl fentanyl (China White).

    B. Two 25 mg bags of 3-methyl fentanyl (China White) would be expected to be lethal to 100% of individuals taking this drug.

    C. The median effective dose (ED50) for 3-methyl fentanyl is 25mg

    D. The median effective dose (ED50) for heroin is 75 mg

    E. The median lethal dose (LD50) for 3-methyl fentanyl is 25 mg or less

    F. The median lethal dose (LD50) for heroin is 75 mg or less

FACILITATORS ANSWER
The CORRECT answer is E. the median lethal dose (LD50) for 3-methyl fentanyl is 25 mg or less, since 50% of people consuming 25 mg or less of China White died.

Choice A is incorrect as the only information provided is that 25mg china white produced death in 50% of the population and we don't know what dose produces death in 100 % of the population so one can't speculate about the relative sensitivity of the population. For example, if 50 mg were found to be the dose that was lethal in 100 % of the population then 100 % of that population could be considered to be "more sensitive" to the effects of China White, despite the LD50 being 25mg or less.

Choice B is incorrect, as we only have information about the LD50 for China White and don't know the slope of the quantal dose response curve to know that two 25 mg bags of 3-methyl fentanyl (China White) would be expected to be lethal to 100% of individuals taking this drug.

Choice C is incorrect because one 25mg bag produced death in 50% of the population indicating that the LD50 was 25 mg or less. Presumably the ED50 for a "desired high"(the specified endpoint) would be less than 25 mg but no information is provided about the dose that produced this effect in 50%of the population or if this is the specified endpoint referred to in determining an ED50.

Choice D is incorrect as the scenario reads that "most" addicts take 75 mg to produce the desired high but no quantitative information is provided to indicate that this is the dose that produces the "desired high" in 50% of the population. Presumably, if the specified effect is the "desired high" and it's produced in "most"(>50%) addicts at 75mg, then it is likely that the ED50 would be lower than 75mg.

Choice F is incorrect, the median lethal dose (LD50) for heroin is 75 mg or less, is incorrect, since the only information provided is that 75 mg of heroin produces a "desired high" in users but there is no indication concerning the lethality at this dose or the dose of heroin that is lethal in 50% of a population of users.

Part 4

Based upon the above case, which of the following statements would be most appropriate?

    A. The therapeutic index of 3-methyl fentanyl is lower than that for heroin

    B. The ED50 of 3-methyl fentanyl is higher than the ED50 of heroin

    C. The LD50 of 3-methyl fentanyl is higher than the LD50 of heroin

    D. The affinity of 3-methyl fentanyl for the mµ opioid receptor is greater than that of heroin

    E. The Emax for 3-methyl fentanyl is greater than the Emax of heroin in a patient population.

FACILITATORS ANSWER

The __most appropriate__ answer is D, the affinity of 3-methyl fentanyl for the mµ opioid receptor is greater than that of heroin. Since the potency of 3-methyl fentanyl is 10,000X than that for heroin, it is most likely that 3-methyl fentanyl has a higher affinity for the mu opiate receptor and can maximally occupy the receptor population at lower doses of drug.

Choice A, the therapeutic index of 3-methyl fentanyl is lower than that of heroin, is incorrect as the therapeutic index by definition is the TD50/ED50 (in this case our toxic effect is death so TD50=LD50). While this answer may seem intuitively to be correct, no absolute quantitative information is provided for the LD50 values for either 3-methyl fentanyl or heroin hence the therapeutic index cannot be calculated.

Choice B, the ED50 of 3-methyl fentanyl is higher than the ED50 of heroin is not correct, as the effects of 3-methyl fentanyl require lower doses than those for heroin.

Choice C, the LD50 of 3-methyl fentanyl is higher than the LD50 of heroin, is incorrect as 25 mg of 3-methyl fentanyl produced death in 50% of the population but 75 mg of heroin was needed to produce a "desired high" in users (presumably not dead users. Consequently, the LD50 of 3-methyl fentanyl would be smaller than the LD50 for heroin.

Choice E, the Emax for 3-methyl fentanyl is greater than the Emax of heroin in a patient population is incorrect, as the Emax (ie. Response in 100% will be identical but the dose required to achieve that Emax will be less for 3-methyl fentanyl than for heroin, hence the difference in ED50)

QUESTION 2
(Teaching Point: Agonist Potency and Efficacy from Graded Dose-Response Curves)

Drug X acts as an agonist at its cognate receptor R1 to elicit a cellular response. Drugs A, B, C and D are all structurally very similar to drug X and all bind to exactly the same binding site on Receptor R1 as Drug X. Figure 1 depicts individual dose-response curves for each of the five drugs as their dose is increased.
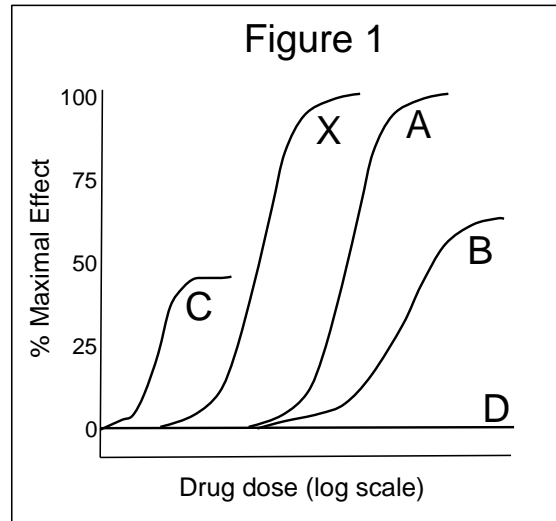
A. Based upon these data, please describe the pharmacodynamic properties of Drugs A, B, C and D <u>relative to Drug X</u> and support your conclusions based on the dose-response data and/or any of the other information provided.

Curve A: ***Full agonist of R1, equi-efficacious to X, but less potent***

Curve B: ***Partial agonist of R1 (by definition less efficacious than X), less potent than X***

Curve C: ***Partial agonist of R1 (by definition less efficacious than X), more potent than X***

Curve D: ***Neutral antagonist of R1, since it neither increases or decreases the biological response, yet binds to the same site on R1 as Drug X***

Question B *(Teaching Point: Pharmacological Antagonism by Neutral Antagonists or Partial Agonists)*

Based on the properties of the Drugs illustrated in Figure 1, use the axes below to provide a graph to illustrate the effects of:

(i) Increasing doses of Drug B on the response of cells stimulated with a single **Emax dose** of Drug X.

(ii) Increasing doses of Drug D on the response of cells stimulated with a single **Emax dose** of Drug X.

Please describe the pharmacodynamic phenomena for each and provide an explanation for the dose-response curves drawn for Drug B and Drug D.
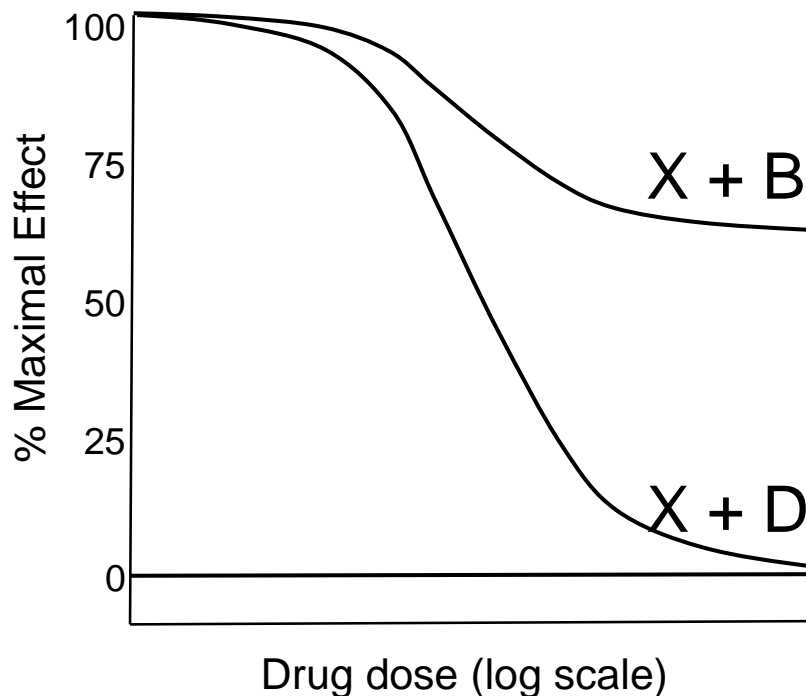
FACILITATORS ANSWER

Drug D is a <u>neutral antagonist</u> of R1 and at increasing concentrations will compete with Drug X for binding to the receptor, thereby preventing the binding of the full agonist and ultimately reducing the biological response to ZERO

Drug B is a <u>partial agonist</u> of R1 and is able to elicit some degree of signaling, although not to the same level as the full agonist. Consequently, increasing concentrations of Drug B will compete with Drug X for occupation of the receptor and will act to reduce the overall level of the biological response, although only to the Emax level of response induced by maximal occupancy of the receptor by Drug B alone (i.e. the partial agonist)

## QUESTION 3 *(Pharmacodynamic Concept: "Spare Receptors" or "Receptor Reserve")*

Drug Y activates its cognate receptor R2 in tissues 1 and 2 to produce cellular increases in cAMP. The maximal efficacy of Drug Y is the same in tissue 1 and tissue 2. The affinity of Drug Y for receptor R2 is identical in both tissues and the receptor density (Bmax) of receptor R2 is identical in both tissues. **In tissue 1**, the K_D of the Drug Y for receptor R2 is equal to its EC50, whereas **in tissue 2** the EC50 of Drug Y is smaller than the K_D of Drug Y for its receptor.

(Teaching Point: Tissue Differences in Spare receptors for the same Receptor Mediated Pharmacological Response)

A. Figure 2 illustrates the dose response relationships of Drug Y in tissues 1 and 2 in the absence or presence of either a low **(1 uM)** or high **(100 uM)** concentration of a **<u>non-competitive irreversible antagonist</u>** of receptor R2.

Please provide an explanation for why the same concentrations of the **<u>non-competitive irreversible antagonist</u>** produces different effects on the dose response curves of Drug Y in tissue 1 versus tissue 2.

Figure 2
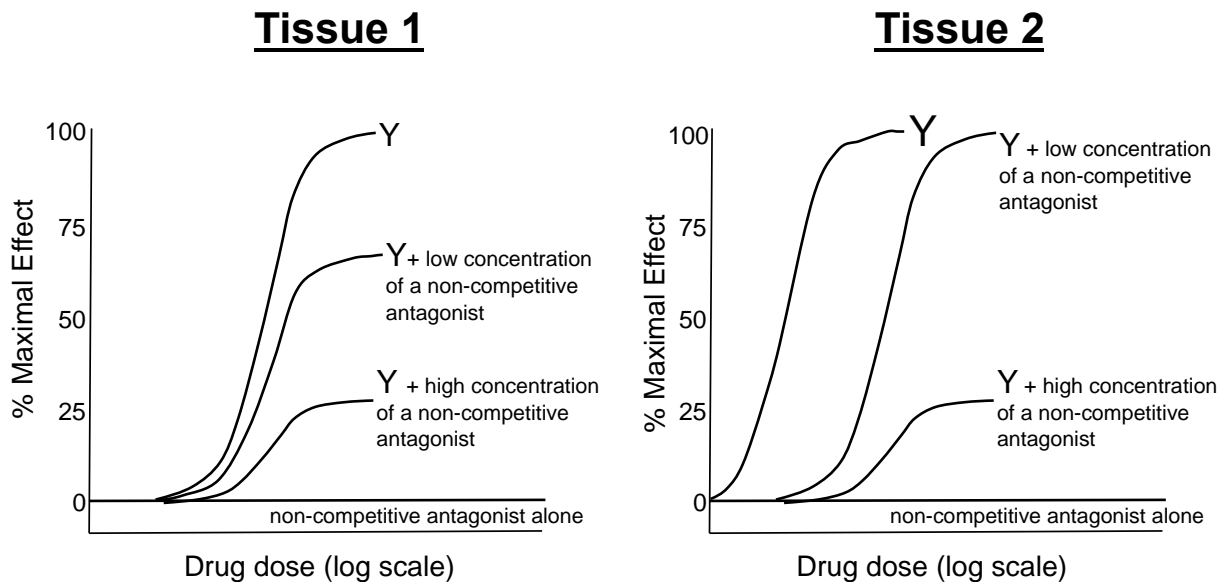
Tissue 1

Tissue 2

FACILITATORS ANSWER

TISSUE 1: The ED50 of Drug Y for receptor R2 is equal to the K_D of Drug Y for the receptor (i.e. the dose required for 50% of the response = the dose required to occupy 50% of the <u>receptors – a system with NO SPARE RECEPTORS</u>).

Accordingly, addition of the two different concentrations of non-competitive irreversible antagonist acts to reduce the number of receptors that are available to bind Drug Y and trigger the biological response, thereby decreasing the maximal biological response (Emax) induced by Drug Y. Note that there is no effect on the potency of Drug Y (i.e. no effect on the ED50).

TISSUE 2: The ED50 of Drug Y for its receptor in Tissue 2 is < the K_D of the drug for its receptor. This defines a system with <u>SPARE RECEPTORS/RECEPTOR RESERVE</u> (i.e. the maximal biological response can be triggered at less than full receptor occupancy).
*At the low concentration of non-competitive irreversible antagonist there will be a reduction in the number of available receptors capable of binding to Drug Y, but because of the spare receptors there is still a sufficient number of receptors available to induce a maximal response (Emax). However, Emax can only be maintained by increasing the fractional occupancy of the receptor, which requires a higher dose of drug (i.e. increase in ED50).*

At the higher concentration of non-competitive irreversible antagonist there will be a greater reduction in the number of available receptors capable of binding to Drug Y. In the example shown, the amount of receptors reduced by the antagonist exceeds the receptor reserve (the number of activated receptors needed to elicit the biological response), as a result there are insufficient numbers of receptors available to induce the maximal response, resulting in a decrease in the Emax.

Part 2 *(Teaching Point: Differences in "Spare Receptors" or "Receptor Reserve" for Different Signaling Pathways Activated by an Identical Receptor Population in the Same Tissue)*

In tissue 1, Drug Y stimulation of R2 receptors concomitantly activates three signaling pathways. In addition to the increases in cAMP mentioned previously, Drug Y stimulation of R2 receptors also increases intracellular Ca^{2+} signaling and the activation of the MAPK cascade. Drug Y is a full agonist and can elicit an Emax response in each of the respective signal transduction pathways, although it exhibits different potencies with respect to its activation of the three pathways, resulting in three distinct EC50s.

As illustrated in figure 3, incubation of tissue 1 with either a low (**1uM**) or a high (**100 uM**) concentration of a **non-competitive irreversible antagonist** results in different effects on the dose response curves of drug Y for the three respective second messenger pathways.

Figure 3
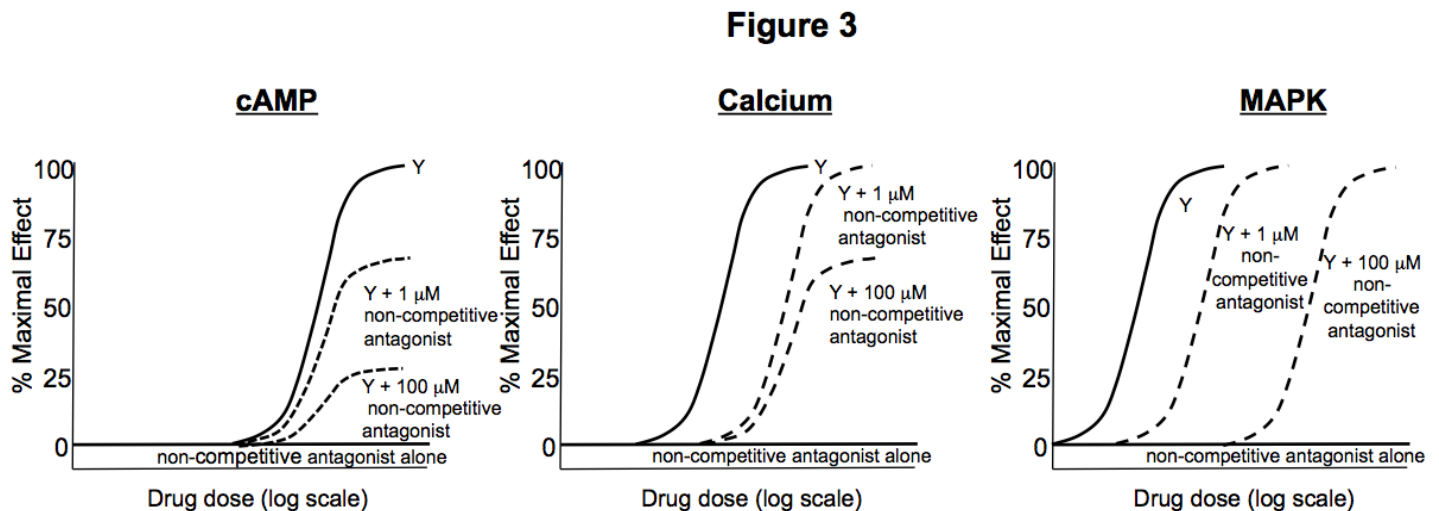
(i) Please provide an explanation for the differences in the dose response curves of Drug Y with respect to the activation of the cAMP, calcium and MAPK signaling pathways observed in the presence and absence of the **non-competitive irreversible antagonist**

(ii) What do these differences in dose–response data indicate about the receptor's respective activation of these three signaling pathways?

FACILITATOR ANSWERS:
In this case, the same receptor (R2) in the same tissue (tissue 1) activates three distinct downstream signaling pathways (cAMP, calcium and MAPK). However, reducing the number of available receptors differentially affects the ability of the receptor to trigger each of the downstream signaling events.

The effects of addition of the irreversible antagonist on the cAMP response indicates that there is no receptor reserve for this pathway (see Part 1), whereas the effects of the irreversible antagonist on the ability of Drug Y to trigger a calcium signal and activation of the MAPK indicates that there are varying levels of receptor reserve in these signaling pathways. (i.e. reducing the number of receptors available for binding to Drug Y does not necessarily reduce the Emax).

Thus, different numbers of the same receptor (R2) are required to be activated to elicit the maximal activation of each of the three different signaling pathways. This likely reflects the different efficiencies with which the receptor is coupled to the downstream signaling components responsible for activating each pathway. Hence, receptor reserve is not just a matter of the number of available receptors in a given cell, but also involves the efficiency by which that receptor couples to the downstream functional output.

***This is a good illustration of how the term "receptor reserve" is somewhat more appropriate than "spare receptor" as the same reduction in receptors results in a differential magnitude of reduction among 3 different downstream messengers. Hence, differences in "receptor reserve"\.*

## QUESTION 4 (*Pharmacodynamic Concept: Homologous and Heterologous Desensitization*)

Drug A is an agonist that binds selectively to its receptor R_A expressed on NCI-H295 adrenocortical cells to induce a cellular increase in cAMP levels. NCI-H295 cells also express receptors R_B and R_C. Drug B is an agonist that binds selectively to the R_B receptor, whereas Drug C is an agonist that selectively binds R_C receptors. Both Drug B and Drug C are chemically distinct from Drug A and neither is capable of stimulating cells to produce cAMP.

The following graphs show the effects of prior exposure of NCI-H295 cells to either Drug A, Drug B or Drug C on the ability of these cells to subsequently respond to acute stimulation with Drug A.
Note: Prior treatment of cells with Drug A did not affect the dose response curves of Drug B, Drug C or any other receptor-mediated responses in these cells (data not shown).

A. What specific pharmacodynamics phenomena are likely to be responsible for the differences in the dose-response curves of Curves 2-5 relative to Curve 1 and what are the likely mechanism involved that are responsible for causing these changes.
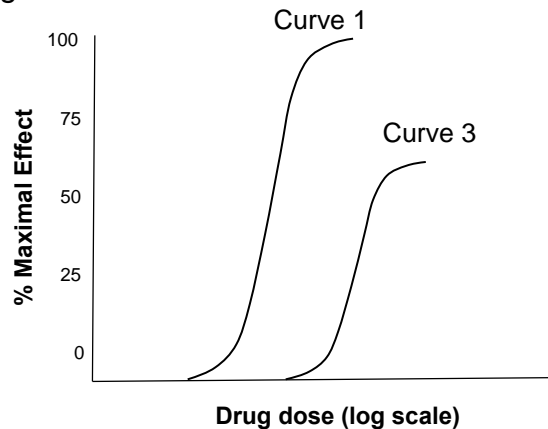
Figure 4A
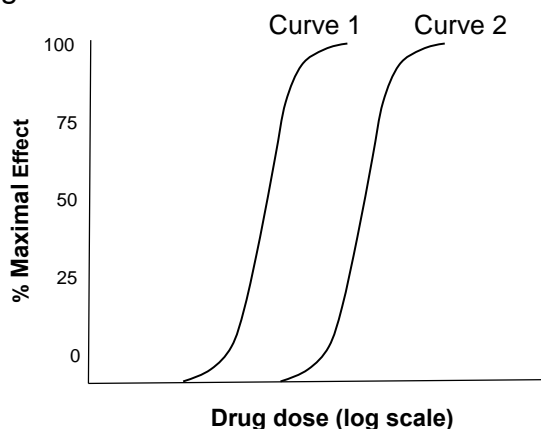
Curve 1 represents the concentration-dependent changes in cAMP in cells acutely exposed to increasing concentrations of Drug A.

Curve 2 represents the concentration-dependent changes in cAMP in cells that were first initially exposed to 10 uM Drug A for a 6 hr period, then subsequently washed, and re-stimulated acutely with increasing concentrations of Drug A.

FACILITATORS ANSWER

Curve 2: <u>*Homologous Receptor Desensitization*</u> *via a reduced responsiveness of receptors to elicit a response (e.g. decreased receptor coupling) and/or a reduction in receptor density that doesn't exceed the reserve of the system for that specific response. This is often mediated by phosphorylation of <u>only</u> agonist occupied receptors by specific kinases (e.g. GRK2/ GRK3,) followed by the binding of β-arrestins to the phosphorylated receptor resulting in a greater degree of desensitization of the receptor. Upon removal of the agonist for a period of time, the receptor can be stimulated to the same extent as before the initial exposure to agonist. This is due to the intracellular dephosphorylation of the receptor and its re-insertion into the membrane or via the production of new receptors, which can then repopulate the plasma membrane. Consequently, this type of desensitization is restricted to <u>only</u> the receptor that was activated by the agonist. This <u>**is not**</u> heterologous desensitization as the questions scenario indicates that prior incubation with A and drug washout does not affect the subsequent dose response of drug B, C or any other receptor mediated events these cells. Only the subsequent response to re-stimulation by Drug A was affected indicating a desensitization specific to the receptor that was initially activated (i.e. Homologous desensitization).*
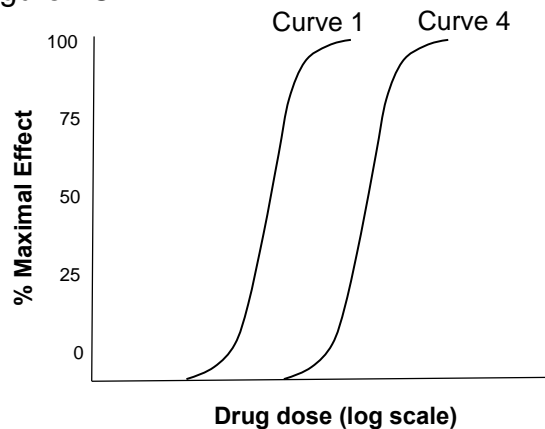
Figure 4B

Curve 1 represents the concentration-dependent changes in cAMP in cells acutely exposed to increasing concentrations of Drug A.

Curve 3 represents the concentration-dependent changes in cAMP in cells that were **repeatedly exposed** to 10 uM Drug A for 3 consecutive 6 hr periods , then subsequently washed and re-stimulated with increasing concentrations of Drug A.

FACILITATORS ANSWER

Curve 3: <u>*Homologous Receptor Desensitization*</u> *via a reduced responsiveness of receptors to elicit a response (e.g. decreased receptor coupling) and/or a reduction in receptor density, which in this case is great enough that <u>it EXCEEDS the reserve of the system for that specific response</u>. Consequently, re-stimulation of the receptor, even at the highest doses of drug A that would occupy the entire receptor population, can never achieve the original Emax of the system. <u>This is not heterologous desensitization</u> as the questions scenario indicates that prior incubation with A does not affect the dose response of drug B, C or any other receptor mediated response in these cells. Only the subsequent response to re-stimulation by Drug A was affected indicating a desensitization specific to the receptor that was initially activated (i.e. Homologous desensitization).*
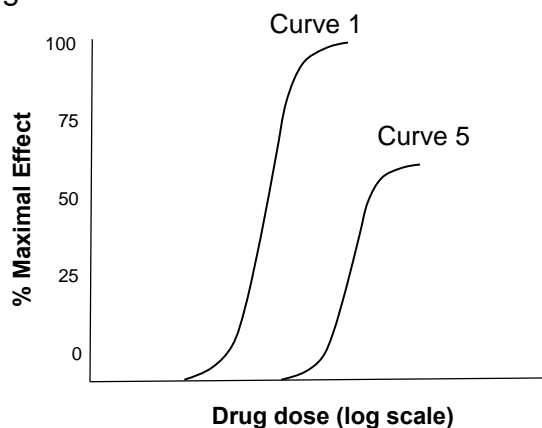
Figure 4C

Curve 1 represents the concentration-dependent changes in cAMP in cells acutely exposed to increasing concentrations of Drug A.

Curve 4 represents the concentration-dependent changes in cAMP in cells that were initially exposed to 10 uM Drug B for a 6 hr period, then subsequently washed, and acutely stimulated with increasing concentrations of Drug A.

FACILITATORS ANSWER

Curve 4: <u>Heterologous *Receptor Desensitization of Receptor A produced by prior activation of Receptor B*</u>. *Likely mediated by Receptor B activation of non-selective kinases (e.g. PKA, PKC) and the non-selective phosphorylation of Receptor A or downstream signaling components in this pathway. These changes could result in down regulation of receptor A, functional uncoupling of receptor A from downstream mediators and/or loss of these components,* <u>*but not to an extent that would preclude that maximal receptor occupancy could still achieve the original maximal cAMP response produced by Drug A.*</u> *Since there may be reduced receptor density or responsiveness, in desensitized systems, higher concentrations of Drug A are required to produce a comparable magnitude of response to that produced by lower concentrations of drug in controls. Consequently, there will be a shift in the DR to the right, and increase in the EC50 and no change in Emax.*

Figure 4D

Curve 1 represents the concentration-dependent changes in cAMP in cells acutely exposed to increasing concentrations of Drug A.

Curve 5 represents the concentration-dependent changes in cAMP in cells that were initially exposed to 10 uM Drug C for a 6 hr period, then subsequently washed, and acutely stimulated with increasing concentrations of Drug A.

FACILITATORS ANSWER

Curve 5: <u>*Activation of Receptor C produces A* Heterologous *Receptor Desensitization of Receptor A by changes to an extent that EXCEEDS the reserve of the system.* *Likely mediated by Receptor C activation of non-selective kinases (e.g. PKA, PKC) and the non-selective phosphorylation of Receptor A or downstream signaling components in this pathway. These changes could result in downregulation of*</u>

receptor A (loss of plasma membrane receptors), functional uncoupling of receptor A from downstream mediators and/or loss of these components. However, in this instance, these changes <u>would be to an extent that EXCEEDS the reserve of the</u> system and thereby precludes the ability of Drug A to achieve its original maximal cAMP response even at maximal receptor occupancy.

Question 5. (Pharmacodynamic Concept: Receptor Supersensitivity)

An individual has been abusing various opiate agonists for an extended period of time and finds he needs to continue to increase the dose of drug to get the same effects as when he first started taking the drug. He hits "rock bottom" after 3 months and decides to enter rehab to "kick the habit". In rehab, he is prevented from taking any opiate agonists and is even administered an opiate antagonist for 2 weeks, the duration of his stay. Since he has done so well in rehab, he is taken off of the opiate antagonist and allowed to go home. On his way home he meets with some old druggie friends who encourage him to "use" again. They tell him that the "stuff" they have is only half the purity of the opiate agonists he had been taking before going to rehab so he can just ease back in. He's getting that old urge back and hesitantly agrees, deciding to inject the same amount of drug that he had been using prior to rehab. Following a single *i.v.* injection he quickly falls to the ground in a deep stupor and a short time later stops breathing (symptoms of an opiate overdose).

    A. What pharmacodynamic phenomena does this above scenario illustrate?

This represents the concept of receptor supersensitivity, which is a compensatory increased responsiveness of a receptor system that occurs in response to a reduction in receptor activation over an extended period of time. This could be produced either by removal of agonist input to a receptor (classic denervation supersensitivity) or precluding receptor activation by the presence of a receptor antagonist.

    B. Use the graph below to illustrate the effects this phenomenon would have on the graded dose response curve of the opiate drug in this individual compared to a control individual.
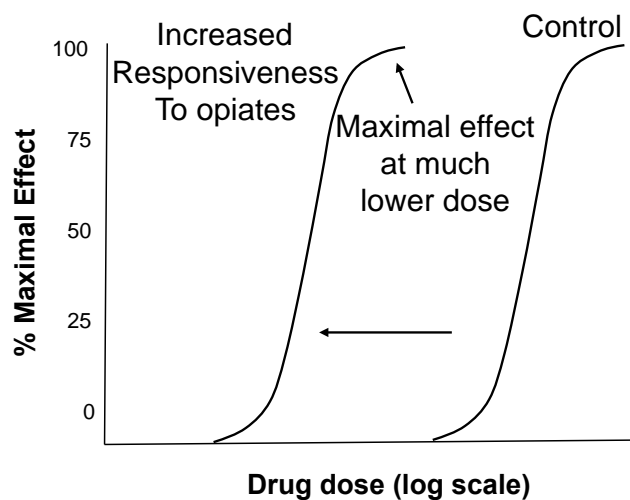

    C. What changes do you think most likely occurred at the cellular level to cause the above phenomenon?

FACILITATOR ANSWER:
In the above scenario, the individual became desensitized to opiates prior to entering rehab. In rehab and following withdrawal of the opiate agonists there likely was a receptor resensitization (with an increased response to opiate agonists relative to the response upon entering rehab). Following two weeks treatment with the opiate antagonist until being released from rehab, the individual would have now developed a receptor supersensitivity, making him even more responsive to any given dose of opiate agonist. This is associated with a <u>shift to the left</u> in the dose response curve. If there were either an increase in receptor density or efficiency of coupling you could occupy a lower fraction of receptors (of the larger or more efficiently coupled) and achieve a comparable response to that at a higher fractional occupancy prior to the supersensitivity (i.e. controls). This is true for all concentrations of drug in a supersensitive system, so the overall dose response curve is shifted to the left. There is a decrease in ED50 and generally no increase in Emax. Given this phenomenon, the individual who injected even a smaller (i.e. less pure) amount of opiate agonist compared to what he was taking prior to entering rehab has an exaggerated response to the drug which likely causes a more profound depression of respiration and results in his death.

Question 6 : (Teaching Point: Interpretation of Quantal Dose Response Curves).
A drug company is performing a large-scale clinical trial to test three new drugs (Drug A, Drug B and Drug C) on their ability to promote weight loss. They test various doses of each drug and for each dose they evaluate what percentage of patients exhibited a 25% decrease in Body Mass Index over a six-month period. During initial pre-clinical testing it was noted that at certain doses these drugs could induce a dangerous increase in blood pressure (i.e. the adverse or "toxic" effect). Hence, in addition, the percentage of patients that experienced a 5 mm Hg increase in blood pressure as a function of drug dose was also determined. The graphs below depict the dose response data for each of the three drugs tested in a patient population for the two different endpoints (i.e. a 25% decrease in BMI & 5mm increase in BP).
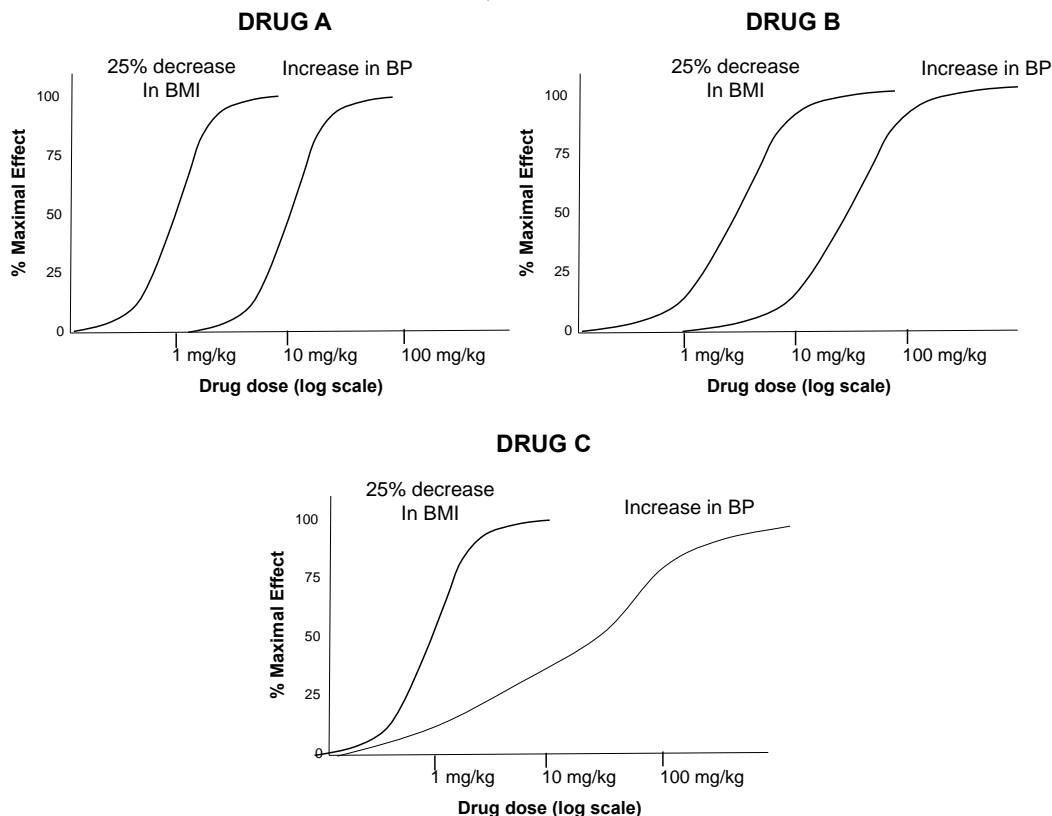
Based on these data:

    A. What are the median effective dose and the median toxic dose for each of the three drugs?

The Median Effective doses: Drug A ED50 = 1mg/kg; Drug B ED50 = 5 mg/kg; Drug C, ED50 = 1 mg/kg.
The Median Toxic doses; A; TD50 = 10mg/kg, B; TD50 = 50 mg/kg, C; TD50 = 50 mg/kg.

    B. What is the therapeutic Index for drugs A, B and C?

The therapeutic indices are (TD50/ED50): Drug A = 10, Drug B = 10; Drug C = 50

    C. Rank the 3 drugs with respect to their therapeutic effect and their toxic effects.

Rank order for therapeutic effect: A = C > B
Rank Order for Toxic Effect: A > B = C

    D. Which of these drugs would you think would be the safest to market and why?

<u>Safest to Market</u>: Drug A with a Therapeutic Index of 10 (equal to that of drug B); since virtually all doses of drug A that produce a therapeutic response <u>do not cause</u> toxic effects in any portion of the population.

    E. Which of these drugs would you have the greatest safety concerns about marketing and why?

<u>Greatest Concern</u>: Drug C; Despite a therapeutic index of 50 (relative to 10 for the other 2 drugs), all doses of drug C that produce a therapeutic effect also cause a toxic effect in a portion of the population.