Clinical Vignettes as a Teaching Tool in Medical Biochemistry

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THE HOW AND THE WHY

- **Purpose of clinical vignettes:**
  - To enhance the learning of concepts in Biochemistry
  - Highlight their clinical relevance
    - Application in clinical diagnosis and management
  - Integrate with other basic sciences (Anatomy, Physiology, Histology, Pathology, Immunology and Pharmacology)

- Posted a week in advance of in-class discussion session
  - Includes 5 – 6 guide questions
    - Designed to stimulate critical thinking

- Student understanding evaluated two ways:
  - At the end of discussion session with two questions (iClicker)
  - During periodic exam for topic covered by vignette

THE HOW AND THE WHY

- **Development of clinical vignettes:**
  - Collaboration between Biochemistry faculty in both TouroCOM-NY campuses
    - Weekly conference calls before and after discussion session
  - Collaboration with faculty in both basic and clinical sciences
    - Weekly meetings before the discussion session
  - Student feedback
    - Survey before the end of the semester

CLINICAL VIGNETTE

- Jonathan is a 22 year-old male who was brought in to the emergency room for progressive shortness of breath and wheezing.
- He has a history of asthma since childhood that has been well-controlled until this past nine months where he has had three visits to the ER for similar asthma attacks. He was treated with tapering doses of oral prednisone each time.
- Jonathan is a nonsmoker but admitted that he is exposed at home to second hand smoke, had recently adopted a cat and mentions that his symptoms seem to be worsening.
- He is currently on an Albuterol inhaler and fluticasone nasal spray but ran out a few days ago and had not refilled the prescriptions.

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- On physical examination, Jonathan was conscious but restless, in moderate respiratory distress with nasal flaring and use of accessory muscles for respiration. There were decreased breath sounds and diffused bilateral expiratory wheezing. Jonathan's one-second forced expiratory volume (FEV_1) normalized to his age, gender and height was at 75% of normal. His oxygen saturation was 70% on room air.
- He was administered O_2 and given 2 mg of nebulized Albuterol and IV methylprednisolone twice over a 30-minute interval. His vital signs did not improve sufficiently, so after 30 min, 500 µg of nebulized Atrovent (ipratropium bromide) was added to the treatment regimen. Jonathan's condition markedly improved in the next three hours and he was discharged with his prescriptions refilled for Albuterol inhaler and fluticasone nasal spray and with instructions on tapering doses of prednisone. He was also given advice regarding triggering agents for his asthma and referred to an allergist for evaluation.

Vital Signs	On admission	30 min	120 min	240 min
Respiratory rate	**46**	**25**	**20**	**18**
Heart rate	**92**	**120**	**90**	**78**
Blood pressure	**150/90**	**135/82**	**125/75**	**120/70**

Suggested guide questions for discussion:

1. How did Albuterol help Jonathan?
2. What is the reason for the increase Jonathan's heart rate at 30 min?
3. How did Atrovent help Jonathan?
4. Why was Jonathan given tapering dose of oral prednisone?
5. Given Jonathan's condition at the ER on admission, would he have had an acid-base disorder at the time? If so, what was it and why did it develop?
6. Aminophylline is a cAMP phosphodiesterase inhibitor. How do you think might it help in an acute asthmatic attack?

Suggested guide questions for discussion:

1. How did Albuterol help Jonathan?

Jonathan received two doses of albuterol over a 30-minute interval. Albuterol is a ***short-acting β_2 adrenergic receptor agonist****, causing bronchodilation and smooth muscle relaxation of the airway.*

Activation of ***β_2 adrenergic receptors*** *(in airway smooth muscles → activates G-protein → release of $G_{s\alpha}$ bound to GTP → interacts with and increases activity of adenylyl cyclase → ↑[cAMP] → cAMP activates PKA → phosphorylation of cellular proteins (e.g., MLCK); cAMP also opens K^+ channels leading to hyperpolarization → decreases intracellular [Ca^{++}] → bronchial smooth muscle relaxation*

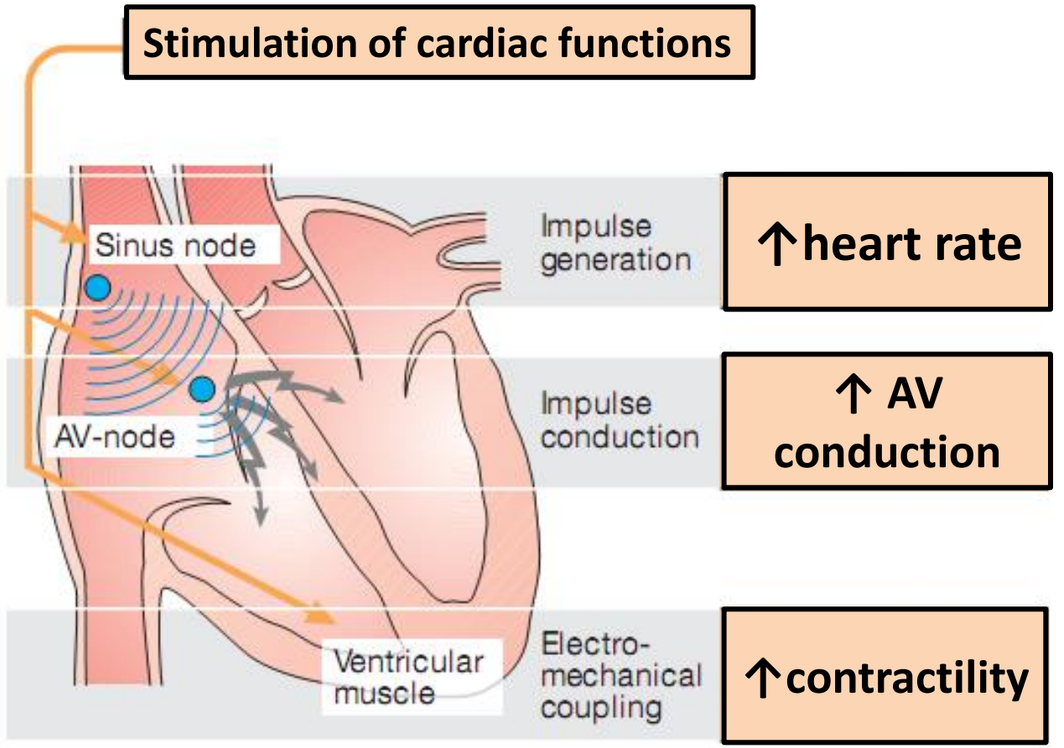
Suggested guide questions for discussion:

2. What is the reason for the increase Jonathan's heart rate at 30 min?

Although Albuterol is a ***selective β_2 adrenergic receptor agonist ,*** *it can* ***act on β_1 adrenergic receptors in cardiac cells*** → ↑ *[Ca^{++}] influx leads to:*

↑ ***pacemaker activity*** ***(*chronotropic effect*)*** ,
↑ *conduction velocity (*dromotropic effect*)* ,
↑ *intrinsic contractility (*inotropic effect*)*

→ ***Resulting in tachycardia***



Suggested guide questions for discussion:

3. How did Atrovent help Jonathan?

*Atrovent (ipratropium bromide) is an **anticholinergic agent** (competitive antagonist of acetylcholine [Ach] for muscarinic receptors) → prevents activation of G_i (↑cAMP) and prevents activation of G_q (↓Ca^{++}) → bronchodilation.*

Atrovent boosts the effect of the initial treatment regimen and helps Jonathan by accomplishing the same effect of bronchodilation as albuterol but through a different pathway.

Signaling via G_q

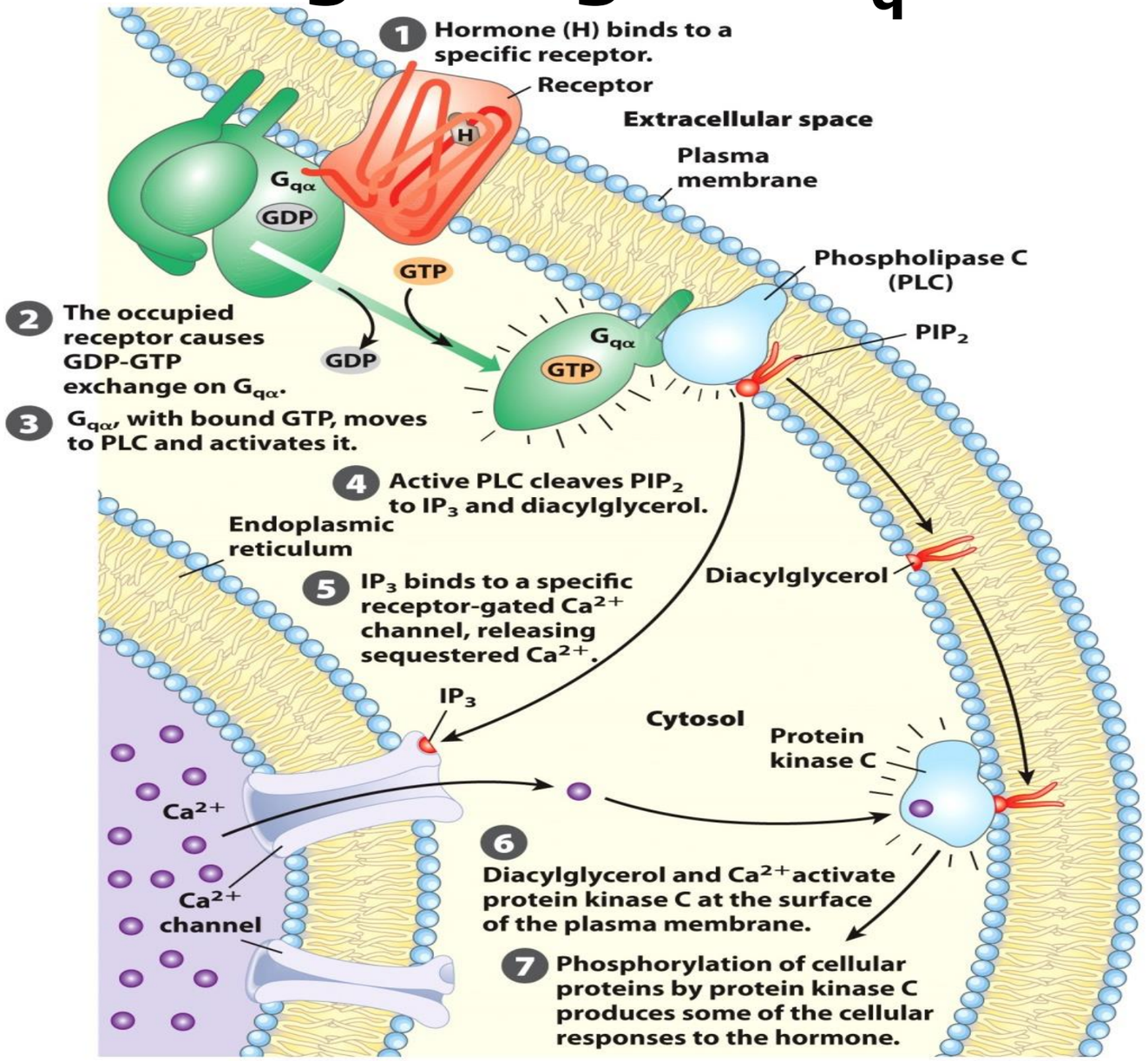


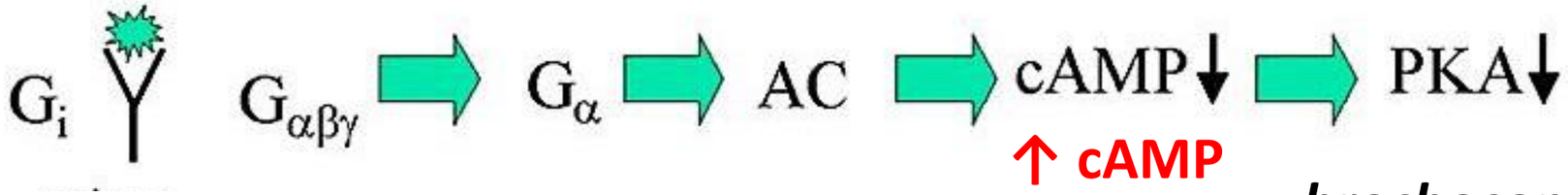
Figure 12-10
Lehninger Principles of Biochemistry, Sixth Edition

Summary of GPCR Signaling

β_2 adrenergic receptor

Albuterol (agonist)

brochodilation



↑ cAMP

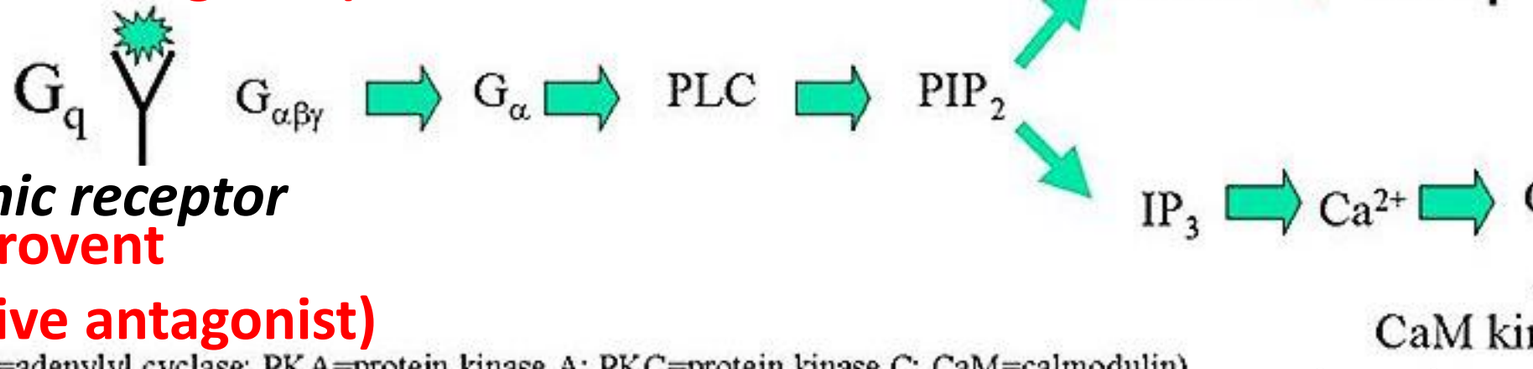
Muscarinic Receptor

Atrovent

(competitive antagonist)

brochoconstriction

bronchodilation



Muscarinic receptor

Atrovent

(competitive antagonist)

↓CaM Kinase

(AC=adenylyl cyclase; PKA=protein kinase A; PKC=protein kinase C; CaM=calmodulin)

brochoconstriction

bronchodilation

Suggested guide questions for discussion:

4. Why was Jonathan given tapering dose of oral prednisone?

Jonathan was given prednisone for its anti-inflammatory effect through inhibition of phospholipase A_2 to impair the production of pro-inflammatory leukotrienes. In addition, prednisone attenuates the desensitization of β_2 adrenergic receptors.

The hypothalamic-pituitary-adrenal axis (HPA) may be suppressed with administration of exogenous glucocorticoids such as prednisone over a long period of time.

Sudden discontinuation or rapid withdrawal of glucocorticoids may result in secondary adrenal insufficiency symptoms (severe fatigue, loss of appetite, weight loss, nausea, vomiting, diarrhea, muscle weakness, irritability, and depression).

Tapering provides adrenal glands with time to return to their regular pattern of secretion and to resume natural function.

Suggested guide questions for discussion:

5. Given Jonathan's condition at the ER on admission, would he have had an acid-base disorder at the time? If so, what was it and why did it develop?

*Jonathan on admission at the ER had RR=46/min (**tachypneic**), HR=92/min, with FEV_1 at 75% of normal and oxygen saturation was 70% (**hypoxic**) on room air.*

FEV_1 is the maximal amount of air one can forcefully exhale in one second converted to % of normal. An FEV_1 75% of normal means Jonathan has mild pulmonary obstruction.

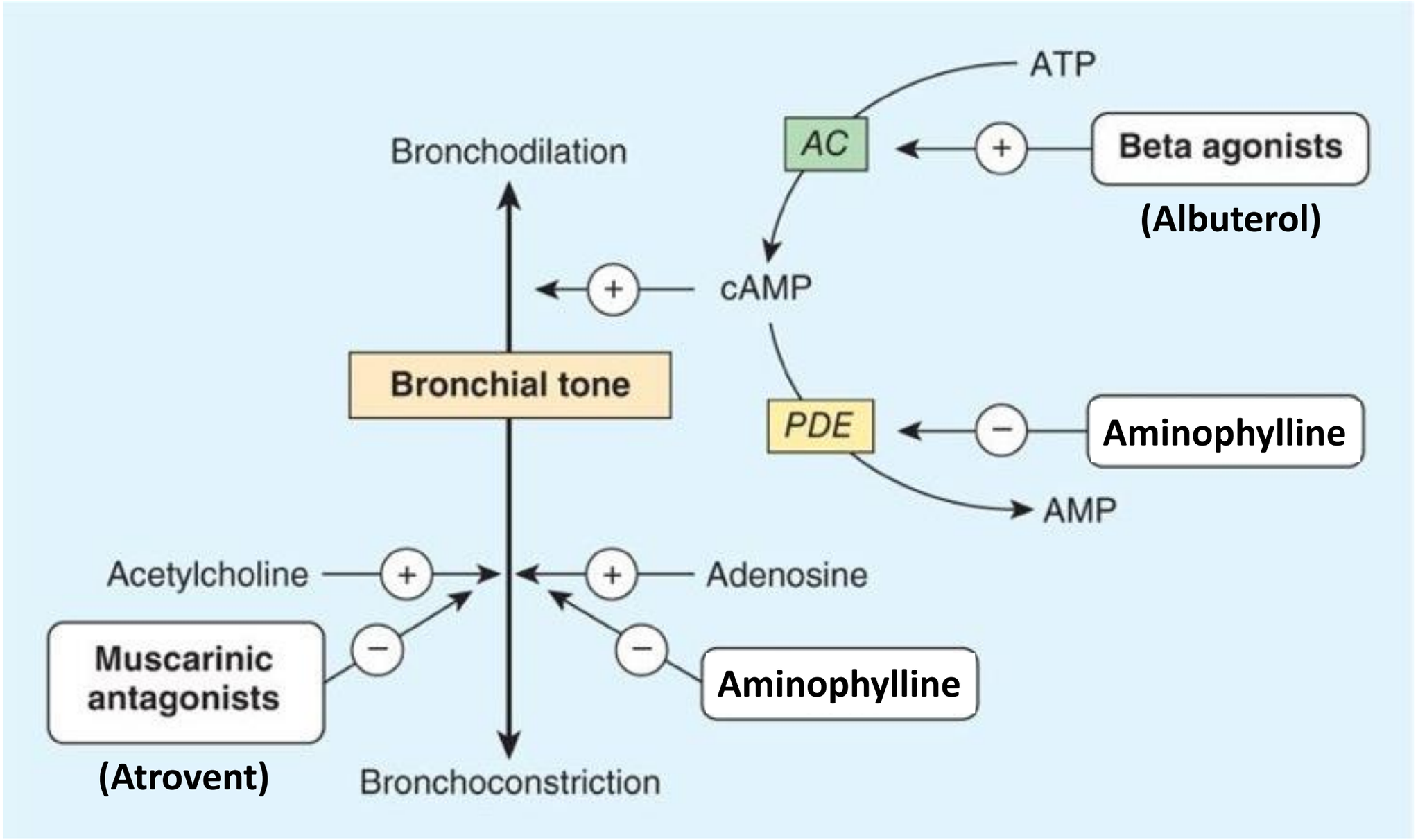
*With RR at 46/min, Jonathan would most likely have **respiratory alkalosis***

*If Jonathan's FEV_1 was <40% of normal, this means Jonathan has severe pulmonary obstruction and would then more likely have **respiratory acidosis***

Suggested guide questions for discussion:

6. Aminophylline is a cAMP phosphodiesterase inhibitor. How do you think might it help in an acute asthmatic attack?

Aminophylline, the cAMP phosphodiesterase inhibitor, will block the phosphodiesterase (PDE) enzyme. This prevents the inactivation of cAMP, and prolongs its downstream effects of smooth muscle relaxation and vasodilation when GPCR-mediated activation of G_s occurs.



Katzung B. Basic and Clinical Pharmacology, 13th ed. (2015)

Question 1

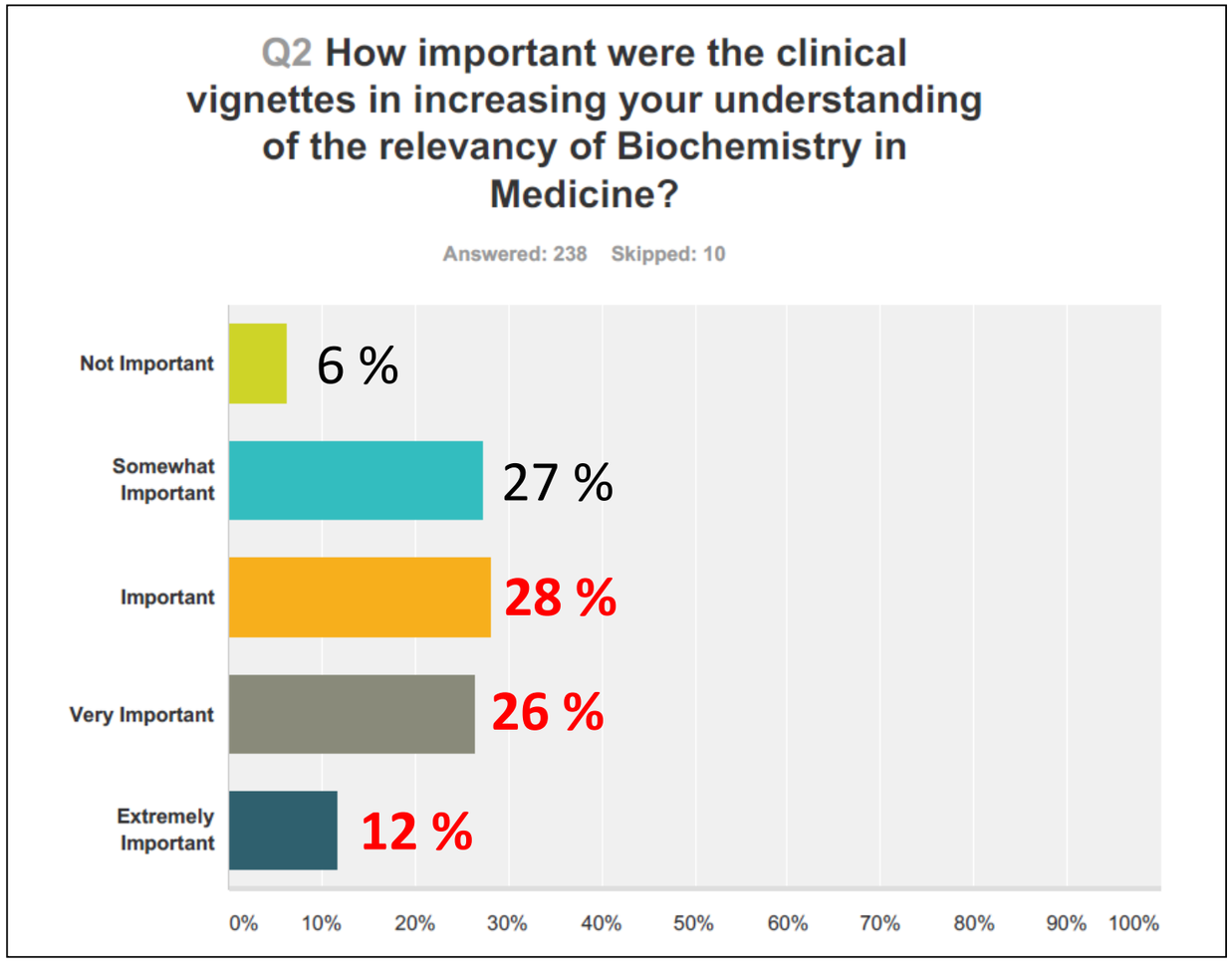
Albuterol is a β2-adrenergic receptor agonist that is recommended in the initial treatment of acute asthmatic attacks. Which of the following is a consequence of Albuterol binding to a β2-adrenergic receptor ?

A. Increased activity of PKA
B. Increased activation of myosin in respiratory smooth muscles
C. Increased intracellular calcium concentration
D. Decreased production of cAMP
E. Decreased cyclic nucleoside phosphodiesterase activity

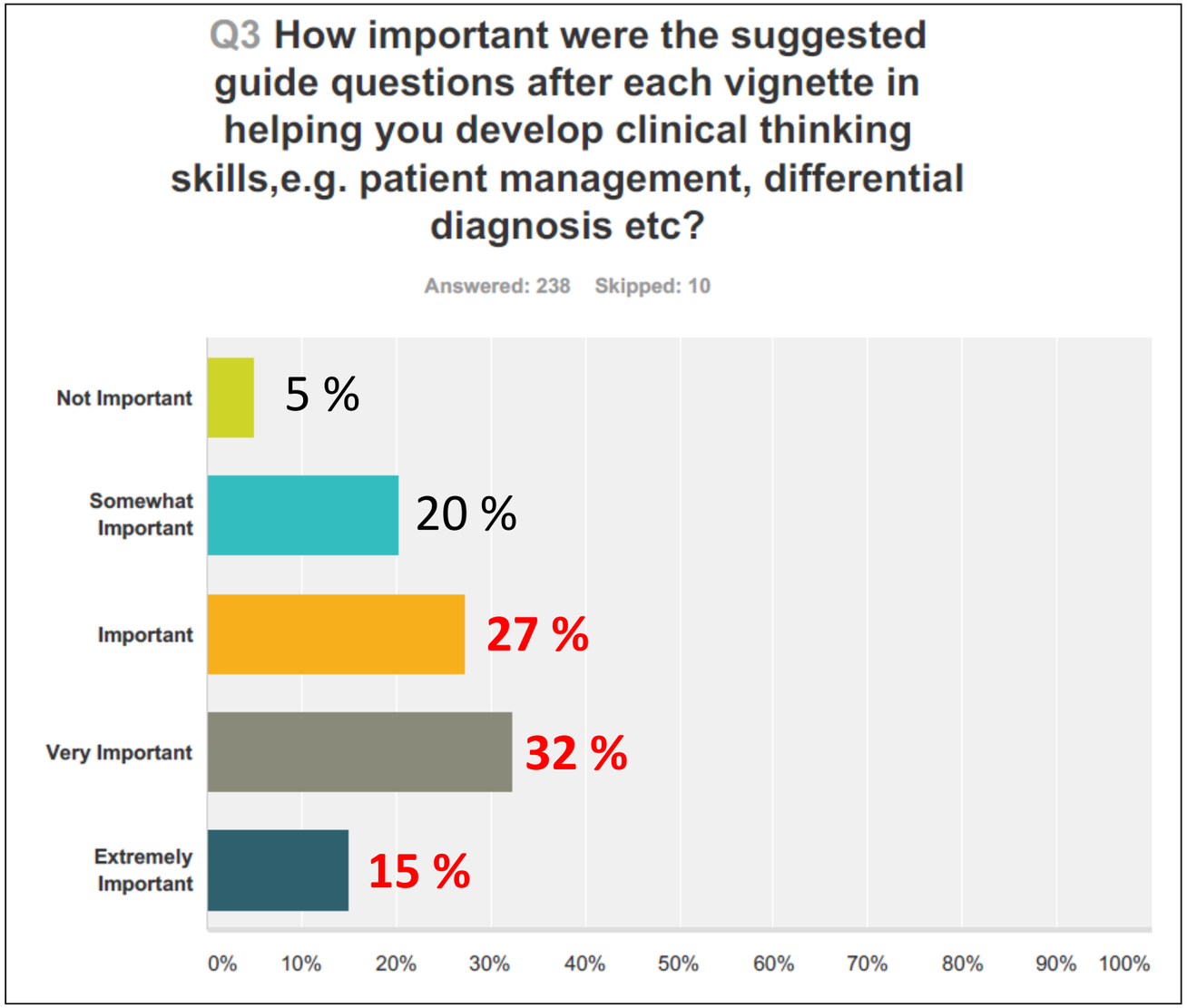
Question 2

The bronchodilator Atrovent is an anti-cholinergic agent. Acetylcholine activates G_i and G_q signaling pathways by binding to muscarinic receptors. Which of the following is a consequence of Atrovent blocking the G_q signaling pathway?

A. Less activation of PKA
B. Increased release of Ca^{2+} from the ER
C. Activation of PKC
D. Increased production of cAMP
E. Decreased activation of CaM-kinases



66 % of students surveyed felt that the clinical vignettes were important in increasing their understanding of the relevancy of Biochemistry in medicine



74 % **of students surveyed felt that the suggested guide questions helped in developing critical thinking skills**

Summary:

- Clinical vignettes are important tools in developing critical thinking skills and in helping students apply biochemical concepts in clinical medicine

- The use of integrative vignettes in first year of medical school is a powerful tool in increasing student interest and understanding of the medical applications of basic science concepts

- These vignettes can be effectively administered in a large group setting with limited faculty

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