

平成14年度大学院医学研究科（1回目）

医学・生物学一般試験（問題用紙1枚、回答用紙2枚）

以下の4問題から2問題を選択して解答しなさい。1問題につき1枚の解答用紙を使用すること。紙面不足の時は裏面使用も可。

問題1. 細胞は相互に結合し、情報交換している。下記の質問に答えなさい。

設問1. 細胞間結合には2つのタイプがある。一つはタイトジャンクション (tight junction)、他はギャップジャンクション (gap junction) と呼ばれる。

両者の違いを簡潔に述べなさい。

設問2. ギャップジャンクションを形成する蛋白質はコネクソン (connexon) と呼ばれる。その簡単な膜内構造の模式図を描き、役割について述べなさい。

問題2. 糖尿病血管合併症の成因の生化学的および分子的機序について述べなさい。

問題3. 化学発がん物質と内分泌かく乱物質の相同と差異について簡潔に述べなさい。

問題4.

設問1. がん分子標的治療法の考え方を従来のがん化学療法との比較の上で解説せよ。

設問2. がんの分子標的として考えられる分子はどのように整理して考える
とよいか？また、その整理に基づき該当する具体的標的分子の代表的な例を
挙げよ。

平成14年度大学院医学研究科(1回目)
外国語試験問題・解答用紙(日本人)

受験番号

以下の文を読み、設問に答えなさい。

Calmodulin (CaM) is a ubiquitously expressed Ca^{2+} binding protein composed of an amino terminal and a carboxy terminal lobe connected by an eight-turn α -helix. CaM binds most target proteins in a Ca^{2+} -dependent manner. ^(A)Both the N terminal and C terminal lobes have two E-F hand that undergo Ca^{2+} -dependent conformational changes that expose hydrophobic binding pockets, allowing binding to amphipathic α -helical domains within the target proteins. In addition to the Ca^{2+} -dependent binding of CaM to target proteins, CaM binds to some proteins in the absence of Ca^{2+} . Several types of Ca^{2+} -independent binding sites for CaM have been reported. One type of Ca^{2+} -independent CaM binding site is an IQ motif (IQXXXRGXXXR). Some IQ motifs, however, can also bind Ca^{2+} -bound CaM (Ca^{2+} CaM). In binding to an IQ motif, Ca^{2+} -free CaM (apoCaM) also undergoes a major conformational change. CaM is both a positive and negative regulator of the cardiac L-type Ca^{2+} channel (DHPR). Elevations in intracellular Ca^{2+} concentration produce a conformational change in CaM, tethered to the channel, producing L-type Ca^{2+} channel inactivation. Zuhlke et al. (1999) have shown that CaM serves as a Ca^{2+} sensor for both positive and negative regulation of the cardiac L-type Ca^{2+} channel. A mutant CaM that cannot bind Ca^{2+} at any of the Ca^{2+} binding sites blocks the effects of Ca^{2+} CaM on the L-type Ca^{2+} channel, suggesting that both the Ca^{2+} -free and Ca^{2+} -bound forms of CaM can bind to this channel. This ability of Ca^{2+} CaM to inhibit the channel appears to be mediated via its binding to an IQ motif in the cytoplasmic carboxy tail of the α_1 -subunit of DHPR. If the isoleucine of this motif is mutated to an alanine, the Ca^{2+} -dependent inactivation is lost, and this unmasks a strong facilitation by CaM. If isoleucine is converted, however, to a glutamate, ^(B)both of the effects of CaM are lost. These findings suggest that apoCaM and Ca^{2+} CaM are binding in the same region of the DHPR or that Ca^{2+} CaM binding sites are allosterically regulated by the binding of apoCaM.

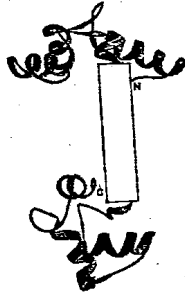
Skeletal and cardiac muscles have different isoforms of the ryanodine receptor (RyR1 and RyR2, respectively). ^(B)In skeletal muscle, only every other RyR1 appears to be coupled to a voltage sensor of the L-type Ca^{2+} channel. Dual regulation by CaM is also seen with RyR1. RyR1 is the major CaM binding protein of sarcoplasmic reticulum (SR) membranes. Tripathy et al. (1995) have shown that CaM bound to SR Ca^{2+} release channel at nanomolar Ca^{2+} concentrations activates the channel. In contrast, CaM bound to RyR1 at micromolar Ca^{2+} concentrations inhibits Ca^{2+} release channel activity. Our studies (1999) demonstrate the existence of a single CaM binding site per subunit of RyR1 at both high and low Ca^{2+} concentrations. RyR1 itself binds Ca^{2+} in the absence of CaM, creating a complicated picture of the response of this channel to Ca^{2+} in the presence of CaM. In the absence of CaM, Ca^{2+} in the 1-300 μM range activates RyR1, but at concentrations of >500 μM it is inhibitory. In the presence of CaM, a biphasic dependence of RyR1 activity on Ca^{2+} is still seen, except both activation and inhibition take place at lower Ca^{2+} concentrations. A mutant CaM that does not bind Ca^{2+} at any of the binding sites is an activator of the channel at all Ca^{2+} concentrations. The results of Fruen et al. (1998) suggest that, in contrast to its interaction with RyR1, apoCaM binds with much lower affinity to RyR2 than to RyR1, and it does not increase RyR2 activity.

(cited from "S.L.Hamilton et al., Calmodulin and excitation-contraction coupling, News Physiol. Sci., 15:281284, 2000")

平成14年度大学院医学研究科(1回目)
外国語試験問題・解答用紙(日本人)

受験番号

設問1. この図は X-ray diffraction により観察した Calmodulin の立体構造を示している。四角の中に本文より推測される構造を書き込みなさい。C は C 端, N は N 端を示す。



設問2. (A)および(B)の下線部分を和訳しなさい。

(A)

(B)

設問3. (C)で示した "both of the effects of CaM" は何を示すか本文に出てくる単語を使い、答えなさい。

設問4. apoCaM の RyR 蛋白質への結合および作用は isoforms によりどのような差異があると記されているか答えなさい。

設問5. Ca^{2+} CaM の L-type Ca^{2+} channel 抑制は channel C 端にある IQ motif への結合によるのであろうと述べられているが、そのような結論を得た実験結果を述べなさい。

平成14年度大学院医学研究科（1回目）
外国語試験問題・解答用紙（日本人）

受験番号

問2. 次の文章を読んで設問に答えなさい。

The epidemiology and molecular biology of colorectal cancer are reviewed with a view to understanding their interrelationship. Risk factors for colorectal neoplasia (a) a positive family history, meat consumption, smoking, and alcohol consumption. Important (b) associations exist with vegetables, nonsteroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy, and physical activity. There are several molecular pathways to colorectal cancer, especially the APC (adenomatous polyposis coli)- β -catenin-Tcf (T-cell factor; a transcriptional activator) pathway and the pathway involving abnormalities of DNA mismatch repair. These are important, both in inherited syndromes (familial adenomatous polyposis [FAP] and hereditary nonpolyposis colorectal cancer [HNPCC], respectively) and in (c) cancers. Other less well defined pathways exist. Expression of key genes in any of these pathways may be lost by inherited or acquired mutation or by hypermethylation. The roles of several of the environmental exposures in the molecular pathways either are established (e.g., inhibition of cyclooxygenase-2 by NSAIDs) (d) are suggested (e.g., meat and tobacco smoke as sources of specific blood-borne carcinogens; vegetables as a source of folate, antioxidants, and inducers of detoxifying enzymes). The roles of other factors (e.g., physical activity) remain obscure even when the epidemiology is quite consistent. There is also evidence that some metabolic pathways, e.g., those involving folate and heterocyclic amines, may be modified by polymorphisms in relevant genes, e.g., *MTHFR* (methyltetrahydrofolate reductase) and *NAT1* (*N*-acetyltransferase 1) and *NAT2*. There is at least some evidence that the general host metabolic state can provide a milieu that enhances or reduces the likelihood of cancer progression. Understanding the roles of environmental exposures and host susceptibilities in molecular pathways has implications for screening, treatment, surveillance, and prevention.

(Cited from Potter, J.D. Colorectal cancer: molecules and populations. J. Natl. Cancer Inst. 91: 916-932, 1999)

設問

1. Colorectal cancerのリスク要因と予防要因は何であると記述されていますか。
2. blood-borne carcinogensはどういう意味でしょうか。
3. (a), (b), (c), (d) に適する語を回答しなさい。
a. _____ b. _____
c. _____ d. _____
4. e.g.はどういう意味でしょうか。
5. The roles で始まる下線部ほどのような意味でしょうか。
6. There is で始まる下線部を日本語に訳しなさい。

平成14年度大学院医学研究科(1回目)

受験番号

外国語試験問題・解答用紙(外国人-英語)

Read the following sentences carefully and answer the questions either in Japanese or in English.

Calmodulin (CaM) is a ubiquitously expressed Ca^{2+} binding protein composed of an amino terminal and a carboxy terminal lobe connected by an eight-turn α -helix. CaM binds most target proteins in a Ca^{2+} -dependent manner. Both the N terminal and C terminal lobes have two E-F hand that undergo Ca^{2+} -dependent conformational changes that expose hydrophobic binding pockets, allowing binding to amphipathic α -helical domains within the target proteins. In addition to the Ca^{2+} -dependent binding of CaM to target proteins, CaM binds to some proteins in the absence of Ca^{2+} . Several types of Ca^{2+} -independent binding sites for CaM have been reported. One type of Ca^{2+} -independent CaM binding site is an IQ motif (IQXXXRGXXXR). Some IQ motifs, however, can also bind Ca^{2+} -bound CaM (Ca^{2+} CaM). In binding to an IQ motif, Ca^{2+} -free CaM (apoCaM) also undergoes a major conformational change. CaM is both a positive and negative regulator of the cardiac L-type Ca^{2+} channel (DHPR). Elevations in intracellular Ca^{2+} concentration produce a conformational change in CaM, tethered to the channel, producing L-type Ca^{2+} channel inactivation. Zuhlke et al. (1999) have shown that CaM serves as a Ca^{2+} sensor for both positive and negative regulation of the cardiac L-type Ca^{2+} channel. A mutant CaM that cannot bind Ca^{2+} at any of the Ca^{2+} binding sites blocks the effects of Ca^{2+} CaM on the L-type Ca^{2+} channel, suggesting that both the Ca^{2+} -free and Ca^{2+} -bound forms of CaM can bind to this channel. This ability of Ca^{2+} CaM to inhibit the channel appears to be mediated via its binding to an IQ motif in the cytoplasmic carboxy tail of the α_1 -subunit of DHPR. If the isoleucine of this motif is mutated to an alanine, the Ca^{2+} -dependent inactivation is lost, and this unmasks a strong facilitation by CaM. If isoleucine is converted, however, to a glutamate, ⁶⁹ both of the effects of CaM are lost. These findings suggest that apoCaM and Ca^{2+} CaM are binding in the same region of the DHPR or that Ca^{2+} CaM binding sites are allosterically regulated by the binding of apoCaM.

Skeletal and cardiac muscles have different isoforms of the ryanodine receptor (RyR1 and RyR2, respectively). In skeletal muscle, only every other RyR1 appears to be coupled to a voltage sensor of the L-type Ca^{2+} channel. Dual regulation by CaM is also seen with RyR1. RyR1 is the major CaM binding protein of sarcoplasmic reticulum (SR) membranes. Tripathy et al. (1995) have shown that CaM bound to SR Ca^{2+} release channel at nanomolar Ca^{2+} concentrations activates the channel. In contrast, CaM bound to RyR1 at micromolar Ca^{2+} concentrations inhibits Ca^{2+} release channel activity. Our studies (1999) demonstrate the existence of a single CaM binding site per subunit of RyR1 at both high and low Ca^{2+} concentrations. RyR1 itself binds Ca^{2+} in the absence of CaM, creating a complicated picture of the response of this channel to Ca^{2+} in the presence of CaM. In the absence of CaM, Ca^{2+} in the 1-300 μM range activates RyR1, but at concentrations of >500 μM it is inhibitory. In the presence of CaM, a biphasic dependence of RyR1 activity on Ca^{2+} is still seen, except both activation and inhibition take place at lower Ca^{2+} concentrations. A mutant CaM that does not bind Ca^{2+} at any of the binding sites is an activator of the channel at all Ca^{2+} concentrations. The results of Fruen et al. (1998) suggest that, in contrast to its interaction with RyR1, apoCaM binds with much lower affinity to RyR2 than to RyR1, and it does not increase RyR2 activity.

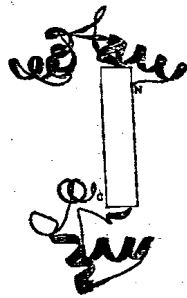
(cited from "S.L.Hamilton et al., Calmodulin and excitation-contraction coupling, News Physiol. Sci., 15:281284, 2000")

平成14年度大学院医学研究科(1回目)

受験番号

外国語試験問題・解答用紙(外国人-英語)

Question 1. The figure shows ternary structure of CaM observed by the X-ray diffraction method. Complete the figure by depicting the three dimensional picture of this protein in a rectangle according to text. C and N represent an amino and a carboxy terminals, respectively.



Question 2. How many calcium ions can a CaM molecule bind? Note with a reason for calculation.

Question 3. What does "(A) both of the effects of CaM" mean? Answer using words mentioned in the text.

Question 4. There are some differences between RyR isoforms on the binding of apoCaM to RyR and function of apoCaM. Note the differences between RyR isoforms.

Question 5. Ca^{2+} -CaM-induced inhibition of L-type Ca^{2+} channel may be attributable to the binding of Ca^{2+} -CaM to IQ motif on C terminal of the channel. What experiment did us lead to such conclusion?

平成14年度大学院医学研究科（1回目）
外国語試験問題・解答用紙（外国人-英語）

受験番号

Problem 2. Read the following sentences and answer the questions either in Japanese or English.

The epidemiology and molecular biology of colorectal cancer are reviewed with a view to understanding their interrelationship. Risk factors for colorectal neoplasia (a) a positive family history, meat consumption, smoking, and alcohol consumption. Important (b) associations exist with vegetables, nonsteroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy, and physical activity. There are several molecular pathways to colorectal cancer, especially the APC (adenomatous polyposis coli)- β -catenin-Tcf (T-cell factor, a transcriptional activator) pathway and the pathway involving abnormalities of DNA mismatch repair. These are important, both in inherited syndromes (familial adenomatous polyposis [FAP] and hereditary nonpolyposis colorectal cancer [HNPCC], respectively) and in (c) cancers. Other less well defined pathways exist. Expression of key genes in any of these pathways may be lost by inherited or acquired mutation or by hypermethylation. The roles of several of the environmental exposures in the molecular pathways either are established (e.g., inhibition of cyclooxygenase-2 by NSAIDs) (d) are suggested (e.g., meat and tobacco smoke as sources of specific blood-borne carcinogens; vegetables as a source of folate, antioxidants, and inducers of detoxifying enzymes). The roles of other factors (e.g., physical activity) remain obscure even when the epidemiology is quite consistent. There is also evidence that some metabolic pathways, e.g., those involving folate and heterocyclic amines, may be modified by polymorphisms in relevant genes, e.g., *MTHFR* (methylene tetrahydrofolate reductase) and *NAT1* (*N*-acetyltransferase 1) and *NAT2*. There is at least some evidence that the general host metabolic state can provide a milieu that enhances or reduces the likelihood of cancer progression. Understanding the roles of environmental exposures and host susceptibilities in molecular pathways has implications for screening, treatment, surveillance, and prevention.

(Cited from Potter, J.D. Colorectal cancer: molecules and populations. *J. Natl. Cancer Inst.* 91: 916-932, 1999)

Questions

1. List up risk factors and beneficial factors of colorectal cancer.
2. What does blood-borne carcinogens mean?
3. Answer appropriate words for (a), (b), (c) and (d), respectively.
a. _____ b. _____
c. _____ d. _____
4. What does e.g. mean?
5. Clarify the meaning of the sentence underlined starting with The roles.
6. Summarize the sentences underlined starting with There is.

平成14年度大学院医学研究科(1回目)

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外国語試験問題・解答用紙(外国人-日本語)

設問1. 以下の文を読み、問に答えなさい。

夏の終わりは、どこか気だるく、もの寂しい気分させるが、この夏はどうもそんな感じがしないまま過ぎた。涼しい日が続いて、暑熱の「よいんにしたる」間もなかったよう。「やらいのあめ」がやんだきのうの朝も、肌寒かった。そうこうしているうちに、暦はもう九月へ。きょうは二百十日。

夏の勢いを弱めてしまった原因は冷たいヤマセ。八月は「まなつひ」がほとんどなかった。青森や八戸では先週、台風が「つうか」したころのわずか一日だけ。太平洋側では稲の育ちが遅れ、三沢では「たいさく」に腰を上げた。海の家などは人も少なく、散々だったよう。

「気になる自然の雲行きだが、それでも季節の交代を告げる生き物たちの営みは確かなようで、何かしらほっとさせる。夕暮れ時、窓の外から聞こえてくる「むしのね」も元気になってきた。風に揺れるコスモスは丈が伸びた。高地から降りてきたトンボたちも、そこちに見える。

<生きて仰ぐ空の高さよ赤蜻蛉(とんぼ)>。一九一〇(明治四十三)年の夏、伊豆の修善寺で「とけつ」した夏目漱石が、ようやく死地を脱したころに詠んだ句。大いなる自然の下に生かされている小さな命に、自らを重ねた「きょうかん」のまなざし。大患の後に仰いだ澄みきった秋空は、漱石の文学の裏りに少なからぬ「ようぶん」となった。

「天高くなる秋は、地上に晴朗の気をみなぎらせてくれる。不順続きだったこの夏を忘れさせる、そんな「ふうけい」が見たい。九月の空よ、冷たく湿ったヤマセを北に吹き飛ばし、ものなりもしゃんとさせてほしい。

(2001/9/1 東奥日報、天地人より)

問1. (A) 下線部分。著者はなぜ「季節の交代を告げる生き物たちの営みにほっとしたのか」50字以内で述べなさい。

問2. (B) 何故このような気にさせるかを夏目漱石の句<生きて仰ぐ空の高さよ赤蜻蛉>の引用との関連から述べなさい。

問3. 1-10の()内のひらがなを漢字にしなさい。

- | | |
|----|-----|
| 1. | 6. |
| 2. | 7. |
| 3. | 8. |
| 4. | 9. |
| 5. | 10. |

平成14年度大学院医学研究科(1回目)

外国語試験問題・解答用紙(外国人-日本語)

受験番号

問題2. さる9月11日にアメリカで同時多発テロがありました。以下の新聞記事(中日新聞・朝刊[平成13年9月15日])は、そのテロに対するアメリカの対応のシナリオです。それを読んで、設問に回答しなさい。

ケース1. 米国は1998年8月、米大使館爆撃事件への報復でアフガニスタン、スーダンを攻撃した。この時の狙いもビンラディン氏だった。今回も同氏に関連する施設に的を絞った限定的な一撃を加える可能性がある。98年は巡航ミサイルを撃ち込んだが、結果としてビンラディン氏らを葬り去ることはできず、効果は不十分だった。(中略)

ケース2. ビンラディン氏をかくまうアフガニスタンに対し「国対国」の形で戦争を仕掛ける可能性も十分ある。大規模なテロに対し強い怒りを持つ米議会では、この選択肢を主張する意見が多数派だ。問題は相当の「返り血」を覚悟しなければならぬ点。戦争が長期化して地上戦に突入すれば米国側の犠牲も避けられない。79年、旧ソ連が侵攻しながら目的を達成できなかった歴史を参考にと、アフガニスタンとの戦いは泥仕合になるリスクが大きい。(中略)

ケース3. 攻撃対象をビンラディン氏と那一味に絞り、ピンポイントの攻撃を加えて暗殺を狙う方法。この場合、テロにテロで報復するという印象が残る、ビンラディン氏側から再報復が図られる可能性も。テロの連鎖を生む悪循環にある現在のイスラエルとパレスチナを連想させる事態に陥る危険が出てくる。(中略)

ケース4. 実質的には米国が単独で攻撃に出るとしても、国際的に大義名分を得るため、連合軍のような形態を米国が求める可能性もある。大統領は13日以来、世界各国や国際機関の首脳と積極的に接触しており、この方法を模索している節もある。湾岸戦争時の多国軍や、コソボ紛争の時の北大西洋条約機構(NATO)軍などのバリエーションが考えられるが、参加国の協力関係を維持できるかがカギ。今は「反テロ」で米国に対する賛同の大合唱になっているが、敵の特定や暗殺方法などをめぐり足並みが乱れる可能性もある。

ケース5. 当面攻撃はせず、外交努力で決着を図る方法。具体的にはアフガニスタンにビンラディン氏の引き渡しを迫りながら、テロの遠因となったといわれるイスラエル、パレスチナの衝突の沈静化を目指すことになる。しかし、各種世論調査で約9割が武力による報復を求めている現状では、国民の理解を得るのは至難の業だ。

設問

問1. 次の言葉の意味を簡潔に説明しなさい。

1. 返り血
2. 泥仕合
3. ピンポイント
4. 悪循環
5. 大義名分
6. 模索
7. 節もある
8. バリエーション
9. 遠因
10. 至難の業

問2. ケース1. の回答例を参考にして、ケース2～5のセッティング、特徴、欠点に関して適当な言葉で答えなさい。

	セッティング	特徴	欠点
ケース1.	98年型	限定的な一撃を加える	効果が不十分
ケース2.			
ケース3.			
ケース4.			
ケース5.			

問3. テロに対する報復の是非、日本の取るべき立場などに関して、あなたの考えを簡潔に述べなさい。