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吹田市基本健診での生活習慣とメタボリックシンドロームに関する研究

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目的　都市住民のメタボリックシンドローム（Mets）有病率とMets定義病態に関連する生活習慣の特徴を性・年齢ごとに評価した。

方法　平成16年度吹田市基本健康診査受診者のうち問診票で有効回答が得られた30～89歳の26,522人の男女を対象とした。MetsはUS National Cholesterol Education Program: Adult Treatment Panel Ⅲの基準を改変して診断した。Mets有病率，Mets有病者での構成因子の有病率を求め，さらにMetsと関連する生活習慣の検討を行った。

結果　30～89歳でのMetsの有病率は，男性19.4%，女性10.7%であった。Mets有病者のうち，若年群では肥満の有病率が高く（30歳代：男性82%，女性90%），高齢群では血圧高値の有病率が高い傾向にあった（80歳代：男性99%，女性98%）。生活習慣では，「他の人より食べる量が多い」「早食いである」「睡眠が不規則である」「立位・歩行時間が1時間未満である」は，男女ともすべての年代でMetsと関連していた。4項目のいずれにも該当しない対象者と1項目該当の対象者のMetsの多変量調整オッズ比は1.29～2.17の値をとり，2個では1.66～4.60，3個では3.13～5.09で，4個すべてに該当する対象者では5.36であった。

結論　Metsの構成因子は年齢により異なっていたが，過食・早食い・不規則な睡眠・運動不足はすべての年代でMetsとの関連がみられ，これらを多く満たす人ほどMetsのリスクが高かったことから，これら4つの項目はMetsの予防・改善の保健指導の項目となりうる生活習慣と考えられた。

キーワード　メタボリックシンドローム，有病率，生活習慣

Ⅰ はじめに

メタボリックシンドローム（Metabolic Syndrome: 以下，Mets）は，肥満，高血糖，脂質代謝異常，血圧高値などの循環器疾患危険因子が集積しやすく，循環器疾患やⅡ型糖尿病を予防する上で目標を定めやすい病態として公衆衛生・予防医学の分野でも注目されている[1]。前向きコホート研究では，Metsの循環器疾患・Ⅱ型糖尿病に対するリスクがこれまでに確認されてきた[2)-8)]。Metsの原因については，遺伝要因と近年の生活習慣における近代化・欧米化といった環境要因の両面の関与が指摘されており，特にアジア人は欧米化した生活習慣によってMetsになりやすい遺伝要因を有していることが知られている[9)10)]。わが国でも，戦後より脂肪摂取量の増加や労働の機械化・交通網の発達による運動量の減少など生活習慣が著しく変化しており，肥満や代謝性疾患の増加も顕著で，Mets有病率の上昇が指摘されている[11)]。しかし，Mets有病率と関連する生活習慣をわ

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が国の都市住民で検討した報告はみられない。

Metsの診断基準はこれまでにいくつか提唱されてきた。代表的なものには，1999年に世界保健機構（WHO）から提唱されたインスリン抵抗性を必須項目とするもの[12]，2001年にUS National Cholesterol Education Program: Adult Treatment Panel Ⅲ（NCEP ATP Ⅲ）の一部として提唱された循環器疾患の予防に焦点をおいたものがあるが[13]，これらに対し，診断基準が複数存在することに対する多岐にわたる評価や診断基準の見直しの必要性も指摘された[14]。2005年に国際糖尿病連合（IDF）から提唱された基準では，ウエスト周囲径による腹部肥満が必須項目とされ，また，従来の項目以外のものも今後研究されるべき項目として考慮されている[15]。2005年に日本内科学会が日本肥満学会・糖尿病学会・動脈硬化学会などの8学会と合同で提唱した日本人のための基準でも，IDFの基準と同様にウエスト周囲径による腹部肥満が必須項目とされている[16]。今後，これらの新しい診断基準を用いた研究が望まれるが，その一方，わが国の過去の健診の多くはウエスト周囲径を項目に含んでいないのが現状である。身長・体重は健診で広く一般に測定され，そこから算出されるBody Mass Index（BMI）は肥満の診断に日常的に使用されている。過去の研究においてNCEP ATP Ⅲの基準のウエスト周囲径による腹部肥満をBMIによる肥満に改変した基準が用いられているが[17]，NCEP ATP Ⅲの基準によると腹部肥満は必須項目ではなく1つの構成因子であり，改変による影響は比較的少ないと思われる。すでに行われた健診のデータを用いてMetsの研究を行う場合には，改変されたNCEP ATP Ⅲの基準を用いるのが現実的な方法と思われる。

著者らは，都市住民を対象に改変したNCEP ATP Ⅲの診断基準を用い，Metsとその構成因子の有病率，Metsに関連する生活習慣を分析し，Metsの予防・改善に役立てることを目的として本研究を行った。

表1　対象者の性・年代別分布

	総数	30歳代	40歳代	50歳代	60歳代	70歳代	80歳代
総数	26 522	2 649	2 697	4 290	9 378	6 055	1 453
男性	8 652	418	504	840	3 649	2 679	562
女性	17 870	2 231	2 193	3 450	5 729	3 376	891

Ⅱ 方　法

（1） 研究の対象

平成16年度吹田市基本健康診査の受診予定者全員（100,885人）にあらかじめ生活習慣問診票を送付し，受診者が記入した問診票は健診の際に医師によって再点検した。健診受診者中の，61,879人の血液検査が同一施設で行われ，このうち30～89歳であり，かつ問診票で有効回答が得られた26,522人（男性8,652人，女性17,870人）を本研究の対象とした。対象者の性・年齢別分布を表1に示す。

（2） 診断基準

NCEP ATP Ⅲ基準の5項目（高血糖［血糖≧110mg/dlまたは治療中］，血圧高値［血圧≧130/85㎜Hgまたは治療中］，高中性脂肪血症［中性脂肪≧150 mg/dl］，低HDLコレステロール血症［HDLコレステロール　男性40 mg/dl未満・女性50mg/dl未満］，肥満［BMI≧25kg/m²］）のうち，3項目以上を満たした場合，Metsと診断した[13]。Metsの構成因子とMetsの有病率を性・年代別に求めた。また，Mets対象者についてのMetsの構成因子の有病率を性・年代別に求めた。問診票での食事・運動・睡眠などの30項目の生活習慣のうち，30～49歳・50～69歳・70～89歳のすべての年代で男女共通してMetsと関連する項目を，ロジスティック回帰モデルを用いて年齢調整して求めた。さらに，それらの生活習慣に1つも該当しない対象者とそれらの生活習慣の組み合わせに該当する対象者のMetsの多変量調整オッズ比を，ロジスティック回帰モデルを用いて性・年齢・飲酒・喫煙を調整して求めた。有意水準は$p<0.05$とし，解析にはSPSS ver11.0を用いた。

Ⅲ 結　　果

Mets の構成因子と Mets の性・年代別有病率を図1に示す。高血糖あるいは血圧高値の有病率は，男女とも年代と共に上昇傾向にあった。高中性脂肪血症では，男性は40歳代から年代と共に低下傾向，女性は上昇傾向にあった。低HDL コレステロール血症では，男性は年代による大きな変化はなく，女性は年代と共に上昇傾向にあった。肥満では，男性は年代と共に低下傾向，女性は上昇傾向にあった。Mets の有病率は，男性は60歳代で最も高く，女性は年代と共に上昇傾向にあった。30～89歳での Mets の有病率は，男性19.4%，女性10.7%であった。

Mets 有病者の Mets 構成因子有病率を性・

図1　メタボリックシンドローム（Mets）の構成因子（5項目）と Mets の有病率

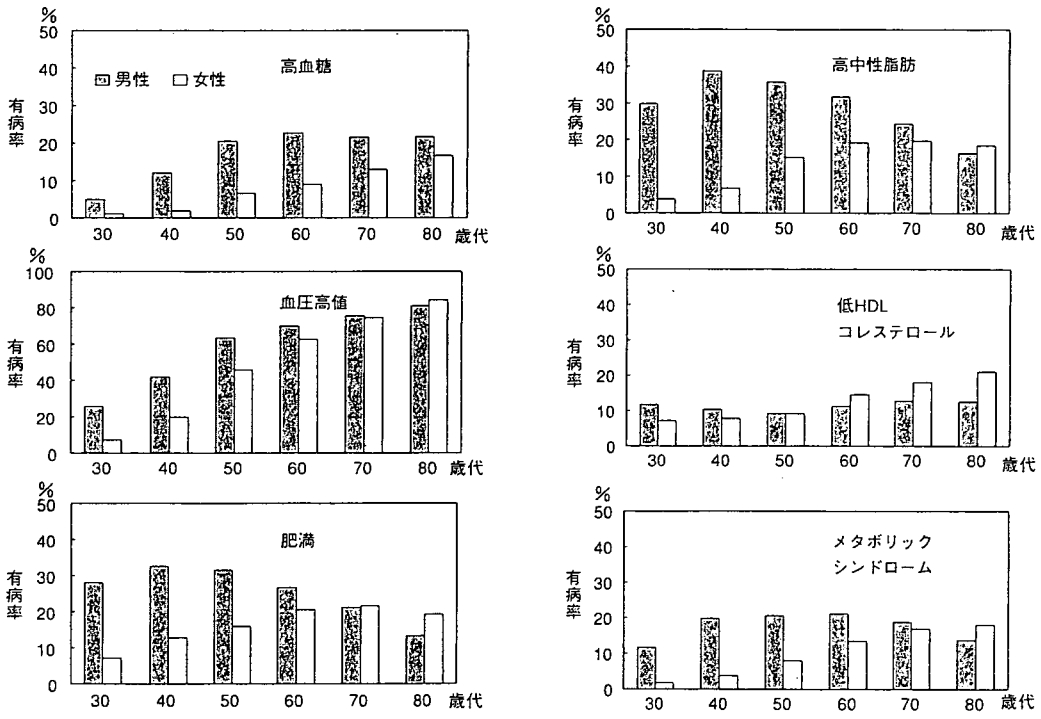


図2　メタボリックシンドローム（Mets）有病者での Mets 構成因子（5項目）有病率

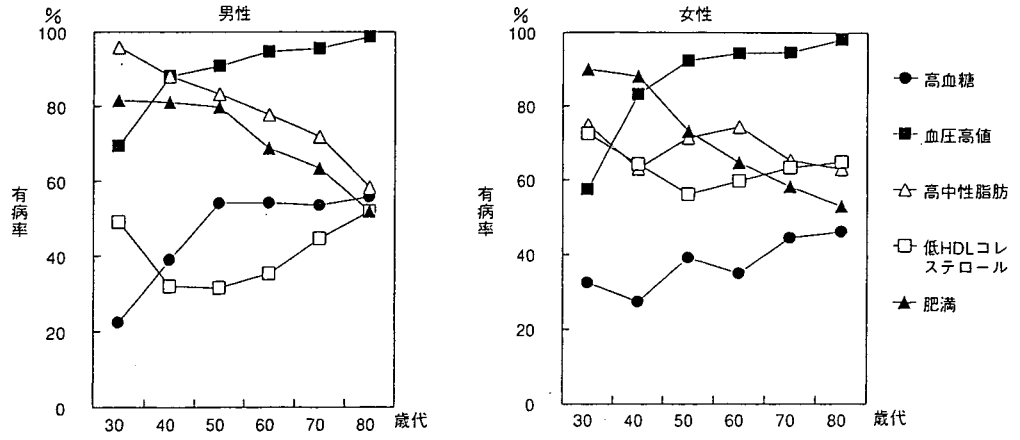


表2　生活習慣の性・年代別割合

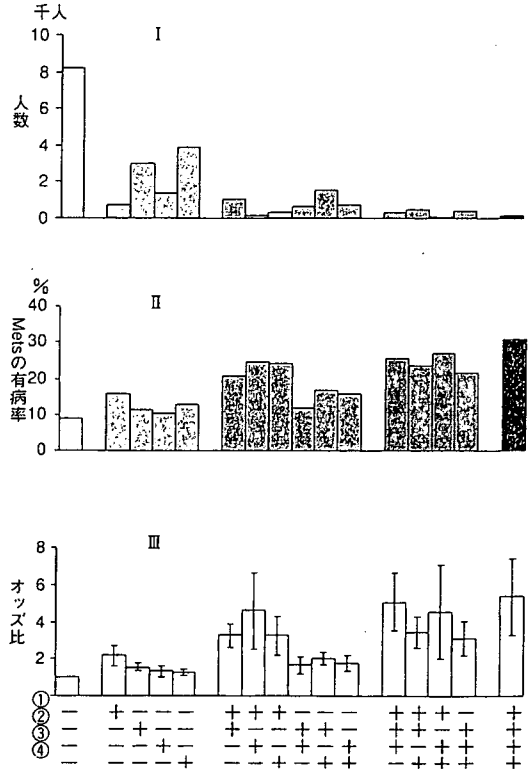
（単位　%）

	総数	30～49歳	50～69	70～89
男性				
他の人より食べる量が多い	15.2	26.7	16.2	10.5
早食いである	35.4	53.9	39.0	24.9
睡眠が不規則である	15.8	31.7	14.4	13.2
立位・歩行時間が1時間未満である	23.4	23.8	20.1	28.1
女性				
他の人より食べる量が多い	14.2	15.5	15.0	11.0
早食いである	32.5	37.1	34.6	23.1
睡眠が不規則である	18.5	20.9	17.5	18.1
立位・歩行時間が1時間未満である	17.2	13.2	14.6	28.3

年代別にグラフ化する（図2）。男性では，血圧高値・高血糖の有病率は年代と共に上昇傾向，肥満・高中性脂肪血症は低下傾向にあった。女性では，血圧高値・高血糖の有病率は年代と共に上昇傾向，肥満は低下傾向にあった。男女ともに共通した傾向として，若年群では肥満の有病率が高く（30歳代：男性82%，女性90%），高齢群では血圧高値の有病率が高いという傾向がみられた（80歳代：男性99%，女性98%）。

生活習慣とMetsの関連の検討では，「他の人より食べる量が多い」「早食いである」「睡眠が不規則である」「立位・歩行時間が1時間未満である」の4項目が，30～49歳，50～69歳，70～89歳のすべての年代で男女ともにMetsと関連していた。この4項目の生活習慣の性・年代別割合を表2に示す。また，この4項目の組み合わせに該当する対象者の分布を図3（Ⅰ）に，それらの対象者でのMetsの有病率を同（Ⅱ）に，4項目のいずれにも該当しない対象者を基準とした4項目の組み合わせ別によるMetsの多変量調整オッズ比を同（Ⅲ）に示す。1個該当する対象者のMetsの多変量調整オッズ比（95%信頼区間）は1.29（1.14-1.46）から2.17（1.74-2.70）の値をとり，2個では1.66（1.28-2.14）から4.60（3.16-6.69），3個では3.13（2.41-4.06）から5.09（3.90-6.66），4個すべてに該当する対象者では5.36（3.85-7.45）であり，該当する生活習慣の個数が多いほどMetsの多変量調整オッズ比が高い傾向がみられた。

図3　メタボリックシンドローム（Mets）と関連のある生活習慣（4項目）の組み合わせ別による対象者人数（Ⅰ），Mets有病率（Ⅱ），Metsの多変量調整オッズ比（Ⅲ）



注　1）生活習慣：①他の人より食べる量が多い，②早食いである，③睡眠が不規則である，④立位・歩行時間が1時間未満である。また，「+」はその生活習慣に該当することを，「−」は該当しないことを示す。
2）Ⅲのグラフ内の縦棒は，95%信頼区間を示す。

Ⅳ 考　察

本研究では，都市住民の検討により，Metsの構成因子が年代によって異なり，若年群では肥満の割合が，高齢群では血圧高値の割合が高かった。このことは，年齢や性によってMetsの病態が異なることを示しており，予防や治療にあたって個々の構成因子の対象が基本になることを示している。

「他の人より食べる量が多い」「早食いである」「睡眠が不規則である」「立位・歩行時間が1時間未満である」は，すべての性・年齢でMetsとの関連がみられ，該当する数が多いほどMetsのリスクが高いことが明らかになった。

「過食」「運動不足」とMetsの関連は過去の研究でも示されたが[18][19]，「早食いである」「睡眠が不規則である」とMetsの関連についての報告は著者らの知る限りこれまでにない。

「早食いである」とMetsの関連の機序は，過去の疫学研究結果，すなわち炭水化物の吸収を遅延させるアカルボースの投与により循環器疾患発症のリスクが半減したこと[20]，摂取後の血糖上昇度の指標であるグリセミック・インデックス（GI値）が高い食品を摂取していた群は心筋梗塞のリスクが高かったこと[21]，糖負荷後血糖の高い群は死亡のリスクが高かったことからも推察される[22]。これらにより，急激な血糖上昇は循環器疾患のリスクを高める可能性が示唆され，また本研究の結果と合わせて，「早食いである」による急激な血糖上昇はMetsを経て循環器疾患発症につながる可能性が示唆される。一方，「早食いである」によって摂食のシグナルが脳の満腹中枢に伝わる前に多量摂取してしまうという機序も考えられる[23]。本研究のデータで，「他の人より食べる量が多い」人の62%が「早食いである」であったことから，両者は同時に起こりやすい行動様式であると考えられる。

「睡眠が不規則である」とMetsの関連の機序は明らかでない。本研究のデータで「他の人より食べる量が多い」「立位・歩行時間が1時間未満である」「現在飲酒・喫煙」のいずれでもない対象者について「睡眠が不規則である」とMetsの構成因子の関連を検討した結果でも，女性で「睡眠が不規則である」と肥満の関連がみられた。

本研究で挙げられた4項目の生活習慣は，すべての性・年代でMetsとの関連がみられたことから，Metsは年齢によって構成因子が異なる病態である一方で，Metsに共通した要因はこれらの生活習慣に起因するものと考えられる。そのため，年齢の幅広い集団を対象とした保健指導でこれらの項目が有用となる可能性が考えられる。また，これらの項目に該当する数が多いほどMetsの割合が高いことから，これらのリスクを減らす指導がMetsの予防・改善につながるものと思われるが，その有用性は今後保健指導の場で検証される必要がある。

謝辞

本研究は，平成16年度厚生労働科学研究費による「脳卒中・虚血性心疾患臨床と地域疫学のデータベースのプラットフォーム化と分子疫学を基軸とした発症機序の解明に関する研究」（主任研究者：友池仁暢）により実施したものである。吹田市医師会前会長菱川音三郎氏をはじめとして，関係各位に謝意を表します。

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OBSTETRICS

A framework for standardized management of intrapartum fetal heart rate patterns

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OBJECTIVE: The purpose of this study was to classify fetal heart rate (FHR) monitor patterns according to risk of fetal acidemia and risk of evolution to a more serious pattern and to use this information to construct a standardized process for FHR pattern management, with the ultimate aim of minimizing newborn infant acidemia without excessive obstetric intervention.

STUDY DESIGN: We have identified 134 FHR patterns that have been classified by baseline rate, baseline variability, and type of deceleration. Based on the best available evidence, we have assigned a risk of newborn infant acidemia or low 5-minute Apgar score to these patterns. We have also evaluated each pattern for the risk that the pattern would evolve further into a pattern with a higher risk of acidemia.

RESULTS: Each FHR pattern has been color-coded, from no threat of fetal acidemia (green, no intervention required) to severe threat of acidemia (red, rapid delivery recommended). Three intermediate categories (blue, yellow, and orange) require escalated informing of appropriate individuals for intervention and resuscitation (obstetrician, anesthesiologist, and neonatal resuscitator) and preparation for urgent delivery (eg, staff and surgical suite availability and conservative techniques to ameliorate the FHR patterns).

CONCLUSION: This framework is applicable potentially to the institutions where it was developed and will need to be modified for other situations, depending on the logistics, facilities, and personnel available. This may provide a framework for developing algorithms for the standardized management of FHR patterns during labor, which can be tested for validity.

Key words: fetal acidemia, fetal heart rate management, intrapartum

Cite this article as: Parer JT, Ikeda T. A framework for standardized management of intrapartum fetal heart rate patterns. Am J Obstet Gynecol 2007;197:26.e1-26.e6.

Despite numerous attempts in the past 30 years, the obstetric community has been unable to reach a broad consensus on a standardized approach to the management of most fetal heart rate (FHR) monitoring patterns. Such disagreement can be seen in the National Institute for Child Health and Human Development (NICHD) publication regarding FHR nomenclature, which contained a small clinical statement.[1] There was consensus that the normal pattern (defined as normal baseline rate, normal [moderate] FHR variability [FHRV], presence of accelerations, and absence of decelerations) confers an extremely high predictability of a normally oxygenated fetus when it is obtained. Thus, no intervention is required for this pattern. At the other end of the spectrum from normality, there was consensus that the pattern of recurrent late or variable decelerations or substantial bradycardia, with absent FHRV, is predictive of current or impending fetal asphyxia so severe that the fetus is at risk of neurologic or other fetal damage or death. The implication is that the fetus should be delivered as soon as possible, unless acidemia can be ruled out rapidly.

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Received Nov. 6; 2006; accepted Mar. 12, 2007.

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0002-9378/$32.00

doi: 10.1016/j.ajog.2007.03.037

Despite the consensus regarding these 2 patterns, the members of the NICHD committee were unable to make overall recommendations for the FHR tracings between these 2 extremes, which represent at least 50% of all intrapartum fetuses, because of the uncertainty in our current state of knowledge about the presumed condition of the fetus in such cases.

The Royal College of Obstetricians and Gynecologists (RCOG) Clinical Effectiveness Support Unit[2] issued a substantial document in 2001 on the use of electronic fetal monitoring, which apparently expanded the guidelines that were proposed by the International Federation of Gynecology and Obstetrics (FIGO) in the 1980s[3] and comprehensively examined the world's literature on the subject. In that document, they classified patterns as normal, suspicious, or pathologic, depending on the incidence of 4 "nonreassuring" or "abnormal" characteristics of the FHR pattern, which they have defined. The guidelines recommended conservative or ameliorating techniques for the suspicious (1 FHR abnormality) categories. For the pathologic categories (≥2 FHR abnormalities) conservative means plus fetal blood sampling are recommended; if fetal blood sampling is not possible, then delivery should be expedited.

The American College of Obstetricians and Gynecologists (ACOG) re-

cently reissued a Practice Bulletin on Intrapartum Fetal Heart Rate Monitoring.[4] Although the preamble purports to describe the management of nonreassuring FHR patterns, the body of the text is concerned mainly with tracing assessment, ancillary testing to rule out acidemia or hypoxia, and "intrauterine resuscitation." The latter techniques are used to ameliorate FHR patterns that are presumed to represent fetal jeopardy.

Although these and other guidelines may be of some use, we have found them to be of limited use in our own labor and delivery room setting. For example, the 4 "abnormalities" of FHR in the RCOG[2] document are neither universally accepted nor equally weighted for degree of risk of fetal jeopardy. Again, fetal blood sampling, which is an important aspect of the RCOG guidelines, is used rarely in the United States today. Fetal stimulation testing is not part of the guidelines. Many of the previously recommended approaches have omitted reference to the likelihood of patterns that evolve to more severe types and have lacked recommendations regarding the speed of clinical reactions to certain more serious patterns to minimize fetal acidemia.

Despite these official positions, we believe that, because of the ubiquity of FHR monitoring, there is an urgent need to standardize management more specifically at this time, with the use of the best available evidence.

In an attempt to develop practical guidelines for the intermediate patterns mentioned in the NICHD document,[1] a multidisciplinary committee at the University of California, San Francisco, produced a 90-page document for the management of all conceivable FHR patterns for internal use. Our intramural committee attempted to determine the severity of FHR patterns that were based on the risk of fetal acidemia by reference to evidence in the literature.[5] This formed the basis for the management recommendations. However after a period of having it available to staff on the labor and delivery unit, we found that is it was infrequently used because of its complexity.

From this vantage point, we now have developed a set of algorithms and recommendations that are much simpler in presentation and therefore may be of more usefulness in practice. As before, the algorithms and recommendations are based on the best available evidence regarding the risk of acidemia of the various patterns, and we have incorporated probability of evolution to more serious patterns as an indicator of urgency of preparation for delivery.

We must stress that this approach was developed in institutions with specific logistics, facilities, and staffing and is highly unlikely to be applicable to other institutions without modification. In addition, although it has been used in our units to demonstrate feasibility, it has not been subjected to appropriate prospective testing, which must be done to determine its validity.

MATERIAL AND METHODS

We constructed a grid of all possible heart rate patterns based on baseline rate (normal, tachycardia, and bradycardia), type of decelerations (early, late, variable, and prolonged), and quantity of variability (undetectable, minimal, moderate, and marked). All definitions were according to the NICHD statement on the nomenclature of FHR patterns.[1] In defining the degree of severity of decelerations, we used the classifications of Kubli et al,[6] in some cases with slight modifications.

Variable decelerations were defined by the National Institutes of Health (NIH) guidelines, and we used the diagram proposed by Chao[7] to quantify them. Severe variable decelerations are ≥60 seconds in duration and <70 beats/min or ≥2 minutes in duration and <80 beats/min. Moderate variable decelerations have a duration of 30 to 60 seconds and are <70 beats/min or ≥60 seconds in duration and <80 beats/min. All other variable decelerations are mild. An unresolved feature of this quantitation is whether the FHR must be below the minimum specified FHR for the whole of the specified time. We have decided arbitrarily that the FHR deceleration must be below this minimum for at least 10 seconds.

Late decelerations, as defined by NIH guidelines, are severe if the decrement of the deceleration is ≥45 beats/min below the baseline, moderate if the decrement is >15 beats/min but <45 beats/min below the baseline, and mild if the decrement is no more than 15 beats/min below the baseline.

Early decelerations were not quantitated because of their rarity and disagreement about the definition in the past.

Prolonged decelerations, as defined by NIH guidelines, require the FHR to be depressed for '2 minutes. *Severe* was defined as <70 beats/min, moderate as between 70 and 80 beats/min, and mild as not <80 beats/min. These are criteria that are similar to those used for quantitating bradycardias.

We initially evaluated each of the patterns on the basis of the risk of fetal acidemia. These associations were made on the basis of a survey of the literature that related FHR patterns to the likelihood of acidemia.[5] The following conclusions were drawn from these associations: (1) The presence of moderate FHRV, even in the presence of decelerations, is associated strongly (98%) with the absence of pH ≤7.15 or Apgar score of <7 at 5 minutes. (2) Minimal or less FHRV with decelerations has a 23% association with pH <7.15 or Apgar score of <7 at 5 min-

TABLE 1
Five gradations of fetal acidemia

Category	Definition
Green	No acidemia
Blue	No central fetal acidemia (oxygenation)
Yellow	No central fetal acidemia, but FHR pattern suggests intermittent reductions in O_2 which may result in fetal O_2 debt
Orange	Fetus potentially on verge of decompensation
Red	Evidence of actual or impending damaging fetal asphyxia

TABLE 2
Risk of acidemia, evolution of FHR patterns to more serious risk, and recommended action

Variable	Risk of acidemia	Risk of evolution	Action
Green	0	Very low	None
Blue	0	Low	Conservative techniques* & begin preparation
Yellow	0	Moderate	Conservative techniques* & increased surveillance
Orange	Borderline/acceptably low	High	Conservative techniques* & prepare for urgent delivery
Red	Unacceptably high	Not a consideration	Deliver

* See Table 3.

utes. (3) The likelihood of acidemia increases with the depth of decelerations, especially with late decelerations, and particularly in patterns with reduced FHRV and more so with absent variability. The risk categories depend on decelerations being recurrent (that is, occurring with ≥50% of contractions in any 20-minute segment).[1]

We then evaluated the risk that the patterns would evolve into a more serious pattern with a higher risk of acidemia. This was based on a conclusion from the previously mentioned report,[5] that, in a fetus with a pattern evolving from normal to decelerative with reduced FHRV, potentially hazardous acidemia develops relatively slowly, over a period of ≥1 hour. It was also based on preliminary work that showed the evolution of patterns in a consecutive series of >1000 fetuses in the last hour before delivery.[8]

Each pattern was classified into 1 of 5 categories for risk of acidemia and evolution to more serious patterns. Other proposed FHR management systems have used 5 categories of risk of either fetal acidemia or hypoxia.[9,10] We made use of the color coding of the Homeland Security Advisory System[11] for the risk of a terrorist attack by categorizing the risk from green (low risk) to red (severe risk). We have substituted the risk of fetal acidemia in these color-coded groups (Table 1).

In place of the protective measures that were proposed by the Homeland Security Advisory System, we have substituted protective measures to avoid acidemia in the fetus. These include a gradation of increasing surveillance and techniques for the amelioration of variant FHR patterns through the various risk groups, with the ultimate protective measure being emergency delivery.

We have not included fetal blood sampling in the management of patterns, because it is rarely used in the United States now; it has been replaced, in general, by observation of the retention of FHRV and accelerations and the use of fetal stimulation testing.

RESULTS

A comparison of the 5 grades of the threat of fetal acidemia and evolution of the pattern is depicted in Table 2; the proposed general actions for each category are shown. The protective measures range from simple observation without intervention for the lowest risk category to emergency operative delivery for the highest risk category. The 3 intermediate categories include such actions as attempts to ameliorate the patterns with conservative techniques (Table 3).

More detailed proposed management and preparations to ensure the ability to mount a rapid response if needed and the availability of appropriate personnel are shown in Table 4.

A grid of each of the possible 134 patterns is shown in Table 5. Each pattern has been color-coded to correspond to 1 of the 5 risk categories; the categories are stratified by quantity of FHRV. In addition, 2 separate categories that are marked variability and sinusoidal patterns are appended.

The need to rule out acidemia by stimulation testing is restricted to relatively few patterns, virtually only those in which there is reduced (or sometimes absent) FHRV and the hope for a vaginal delivery in the near future. Thus, we would accept fetal stimulation testing (either tactile or vibroacoustic stimulation) as appropriate in certain cases of the fourth category (orange) or for uncertain or puzzling patterns.

COMMENT

As noted earlier, few publications on the management of FHR patterns specify what interventions should be applied to specific FHR patterns and particularly what interventions are required to deliver a fetus in a timely fashion to avoid continuing intrauterine hypoxia. This framework has been developed to be a first step in guidelines for optimal FHR pattern management.

The proposed framework has several potential advantages over previous systems. For example the FIGO[3] and RCOG[2] approaches advise action for certain patterns that contain FHR characteristics for which there is not universal agreement regarding immediate fetal

TABLE 3
Conservative ameliorating techniques for the modification of variant FHR patterns

Position change
Hyperoxia
Correct hypotension
Adequate intravascular volume
Correct excessive contractions (eg, decrease oxytocin)
Avoid constant pushing
Tocolysis
Amnioinfusion to correct amniotic fluid deficit

TABLE 4
Proposed management of the color-coded categories

Category	Conservative techniques	Operating room	Obstetrician	Anesthetist	Newborn infant resuscitator	Location of patient
Green	No	—	—	—	—	—
Blue	Yes	Available	Informed	—	—	—
Yellow	Yes	Available	At bedside	Informed	Informed	—
Orange	Yes	Immediately available	At bedside	Present	Immediately available	Operating room
Red	Yes	Open	At bedside	Present	Present	Operating room

jeopardy. The current proposal allows more selective approaches to each individual FHR pattern and still gives guidelines to the risk of fetal acidemia and rapidity with which preparations for delivery should be made based on the likelihood of evolution of the pattern to a pattern with a higher risk of acidemia.

The proposals in the system of Keith et al[9] have the benefit of having been subjected to validation is a nonrandomized trial and appear to minimize fetal acidemia, while also minimizing unnecessary obstetric intervention. However, the program requires special equipment that is not yet available to the practitioner.

Further ancillary testing has been proposed recently for patterns in which it is believed that the risk of acidemia is uncertain (eg, fetal pulse oximetry[12] and ST-segment analysis[13]). Pulse oximetry has not achieved acceptance as an ancillary technique to FHR monitoring in the United States because of unclear results of efficacy in trials.[14] ST-segment analysis in association with FHR monitoring has been tested widely in Europe, and trials have shown a reduction in newborn infant acidemia and no adverse effect on obstetric interventions.[13] It has been ap-

TABLE 5
Risk categories for fetal acidemia related to FHRV, baseline rate, and presence of recurrent decelerations

Variable	No	Early	Mild VD	Moderate VD	Severe VD	Mild LD	Moderate LD	Severe LD	Mild PD	Moderate PD	Severe PD
Moderate (normal) variability											
Tachycardia	B	B	B	Y	O	Y	Y	O	Y	Y	O
Normal	G	G	G	B	Y	B	Y	Y	Y	Y	O
Mild bradycardia	Y	Y	Y	Y	O	Y	Y	O	Y	Y	O
Moderate bradycardia	Y	Y			O		O	O			O
Severe bradycardia	O	O			O			O			O
Minimal variability											
Tachycardia	B	Y	Y	O	O	O	O	R	O	O	O
Normal	B	B	Y	O	O	O	O	R	O	O	R
Mild bradycardia	O	O	R	R	R	R	R	R	R	R	R
Moderate bradycardia	O	O			R		R	R			R
Severe bradycardia	R	R			R			R			R
Absent variability											
Tachycardia	R	R	R	R	R	R	R	R	R	R	R
Normal	O	R	R	R	R	R	R	R	R	R	R
Mild bradycardia	R	R	R	R	R	R	R	R	R	R	R
Moderate bradycardia	R	R			R		R	R			R
Severe bradycardia	R	R			R			R			R
Sinusoidal						R					
Marked variability						Y					

B, blue; *G*, green; *LD*, late decelerations; *O*, orange; *PD*, prolonged decelerations; *R*, red; *VD*, variable decelerations; *Y*, yellow.

TABLE 6
Fetal pH in late decelerations with decreased FHRV

Late decelerations	Mean pH	1 SD	2 SD
Mild	7.23	7.18	7.13
Moderate	7.16	7.12	7.07
Severe	7.09	7.04	6.99

Adapted from Paul RH, Suidan AK, Yeh S, Schifrin BS, Hon EH. Clinical fetal monitoring: VII, the evaluation and significance of intrapartum baseline FHR variability. Am J Obstet Gynecol 1975;123:206-10 (with permission).

proved recently by the Food and Drug Administration for marketing in the United States.

We believe this proposed standardization of management is required even while awaiting agreement on the acceptability of these ancillary techniques, because of the relatively long delay in the widespread introduction of these techniques. If the ancillary techniques are finally accepted, they will fit readily into these management approaches.

The ACOG[4] proposal rightly points out the relative paucity of objectively collected data for many aspects of FHR monitoring and interpretation and does not really give specific recommendations for actual management but rather gives the range of options that are currently acceptable. The ACOG guideline is quite general in many ways and of limited use to practitioners who seek specific guidance.

A number of aspects of FHR pattern management have been omitted from this framework, primarily to maintain simplicity. Our assumption is that reduced variability in the absence of decelerations is not due to hypoxia. Periods of reduced variability (eg, because of fetal sleep cycles) may last over an hour. A further point is that, in the setting of reduced variability, the presence of accelerations of the FHR (either provoked or spontaneous) gives assurance of absence of significant fetal acidemia.

A further omission from the proposal is any distinction between FHR patterns in the first and second stages of labor. Decelerations are more common in the second stage, and management in this stage is often modified by the fact that delivery may be achieved by an operative vaginal delivery, instead of a cesarean section.

In the construction of the color-coded grid, certain decisions had to be made with regard to the risk of fetal jeopardy. As noted earlier, there is good evidence that the normal trace confers a high chance of the absence of fetal acidemia and that other patterns (eg, the absence of FHRV and deep decelerations) are associated with an unacceptably high risk of acidemia. However, the many patterns between these 2 extremes have varying risks, for which there are limited data in the literature. Even where we do have data, there is still the need to make a decision regarding what level of risk is acceptable. We have used lower limit thresholds of pH 7.1 and base excess of −12 mEq/L in umbilical arterial blood as acceptable. These are 2.5% or 2 SD below the mean for normal newborn infants[15] and are well above the values in cases in which fetal hypoxic damage is seen.[16]

An example of the decision-making process in the application of risk to various patterns can be seen by reference to the categories of severity of late decelerations with reduced or absent FHRV. Data from the paper by Paul et al[17] have been abstracted from their figure that relates to fetal scalp blood pH to severity of late decelerations and are shown in Table 6. Mean values are given together with estimated SDs below the mean.

Severe late decelerations with reduced FHRV have mean pH below our threshold of 7.1 and warrant expeditious delivery. Moderate late decelerations with reduced FHRV have an acceptable mean pH, but in this category 2.5% of fetuses will have a pH <7.07, which is below our acceptable range. The 7.1 threshold lies between 1 and 2 SDs and represents perhaps 10% of fetuses in this category. Therefore, a decision must be made whether to expedite delivery in all 100% of these cases to prevent unacceptable acidemia in the 10%.

Mild decelerations with reduced FHRV present a more difficult quandary. Fetuses are 97% likely to have a pH >7.13. However, there will be approximately 1% of fetuses below our pH threshold of 7.1. Should we expeditiously deliver all 100% of these babies for the 1% who actually need it?

There is obstetric precedent for acceptable risk. For example, we offer amniocentesis for karyotyping in mothers where the risk of aneuploidy is <1%. The morbidity for well-managed vaginal breech delivery is <1%, yet patients most now have cesarean delivery. The risk of uterine rupture in vaginal birth after cesarean candidates is approximately 0.5%, but vaginal birth after cesarean birth is fast disappearing. With this in mind, we tentatively propose that a threshold risk of pH 7.1 be set to capture all but 1% of babies; we believe most of these in tracings with reduced FHRV with pH <7.1 will be relatively close to this value and >7.0.

It should be clear that the guidelines must be modified for use in institutions other than our own and may need to be modified at different times of the day, as logistics change. It should also be obvious that this is a preliminary approach, which, although it may appear to work in principle, will need to be subjected ultimately to appropriate testing.

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Tohoku J. Exp. Med., 2007, 212, 151-157

Prenatal Exposure to 3,3′,4,4′,5-Pentachlorobiphenyl (PCB126) Promotes Anxiogenic Behavior in Rats

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ORITO, K., GOTANDA, N., MURAKAMI, M., IKEDA, T., EGASHIRA, N., MISHIMA, K. and FUJIWARA, M. *Prenatal Exposure to 3,3′,4,4′,5-Pentachlorobiphenyl (PCB126) Promotes Anxiogenic Behavior in Rats.* Tohoku J. Exp. Med., 2007, **212** (2), 151-157 —— Polychlorinated biphenyls (PCBs) are environmental contaminants that have adverse effects on the endocrine and nervous systems. As they are still detected in breast milk and adipose tissue in humans, the accumulated PCBs may transfer from mothers to children and damage central nervous system. It is revealed from epidemiological studies that cognitive and motor functions were damaged in children born to mothers who ingested PCBs-contaminated foods. However, it remains unclear whether prenatal exposure to PCBs affects emotionality. In the present study, we therefore examined the effect of prenatal exposure to 3,3′,4,4′,5-pentachlorobiphenyl (PCB126) on emotionality in rats by focusing on anxiogenic behavior and response of the hypothalamus-pituitary-adrenal axis to stress. Pregnant rats were treated orally with PCB126 at a dose of 30 μg/kg or corn oil, its vehicle, on gestational day 15, and their male offspring were subjected to the following experiments at 4-5 weeks old. In an open field test, rats with prenatal exposure to PCB126 showed anxiogenic behavioral responses, including decrease in time spent in the center of an open field and the number of rearings and extension of grooming duration. Interactive behavior, which is an index of anxiety level, was shortened in the social interaction test. The increase in the serum corticosterone level induced by forced swim stress was facilitated by prenatal exposure to PCB126. This evidence suggests that PCB126 may exert anxiogenicity on the offspring of exposed dams, and dysfunction of the hypothalamus-pituitary-adrenal axis may at least in part contribute to this abnormality. ——— 3,3′,4,4′,5-pentachlorobiphenyl (PCB126); prenatal exposure; anxiogenic; corticosterone

Polychlorinated biphenyls (PCBs) are widespread persistent environmental contaminants. Because of their stability and lipophilic properties, PCBs are accumulated by biological magnification; indeed, residues of PCBs have been detected in humans, fish, and wildlife (Kalantzi et

Received March 20, 2007; revision accepted for publication April 23, 2007.
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al. 2004; Carlson and Hites 2005; Cok et al. 2007). Epidemiological studies revealed that perinatal exposure to PCBs exerted a developmental neurotoxicologic effect on humans (Nakai and Satoh 2002; Schantz et al. 2003). In Taiwan, pregnant mothers were accidentally exposed to PCBs through the ingestion of contaminated rice oil and neurodevelopmental abnormalities were observed in their offspring (Chen et al. 1992). Children born to mothers who ingested PCB-contaminated fish also exhibited neurological impairment (Jacobson and Jacobson 1996). This evidence confirmed the long-term impact of PCBs on cognitive deficits and intellectual dysfunction. In experimental studies, the effects of PCBs on learning and memory, and the mechanisms of dysfunctions have been reported (Gilbert and Crofton 1999; Faroon et al. 2001); however, the effect of prenatal exposure to PCB with special reference to the impact on emotionality has not been explored in-depth to date.

3,3′,4,4′,5-pentachlorobiphenyl (PCB126), benzene rings of non-*ortho*-substituted PCB, may assume a planar configuration and have been suggested to be dioxin-like, the most toxic PCB congener (Safe 1990). PCB126 increased adrenocorticotropic hormone in pituitary cells that stimulate the secretion of corticosterone from the adrenal cortex (Bestervelt et al. 1998). PCB126 raised cortisol levels in human adrenocortical cells (Li and Wang 2005). Serum corticosterone was increased by exposure to Aroclor 1254, a PCB mixture which contains PCB126 (Kodavanti et al. 2001), in mice and rats (Sanders et al. 1974; Miller et al. 1993). Thus, PCB126 elevates serum corticosterone/cortisol levels in both direct and indirect manners. Recently, Zagron and Weinstock (2006) revealed that high-level maternal corticosterone was responsible for the anxiogenic properties of offspring. From this evidence, we hypothesized that maternal exposure to PCB126 would cause emotional disturbance in offspring.

In the present study, rats were exposed to PCB126 during pregnancy, and the emotionality of their offspring was evaluated in terms of anxiogenicity. Moreover, the effect of prenatal exposure to PCB126 on the HPA axis was examined by measuring serum corticosterone levels before and after forced swim stress. Prenatal exposure to PCBs possibly exerts motor dysfunction (Chen et al. 1985; Nguon et al. 2005); thus, the effect of prenatal exposure to PCB126 on motor coordination was also examined.

Materials and Methods

Subjects

Twenty 10-week-old female and ten 12-week-old male Sprague-Dawley rats were purchased from SLC, Japan and acclimated for 1 week prior to the start of the experiment. Rats were housed in a cage at 23 ± 2°C, 60 ± 10% humidity, and with lights on daily from 7:00 a.m. to 7:00 p.m. in a controlled room, and received laboratory chow and water *ad libitum*. Two female rats were cohabited overnight with a male rat. Females with sperm in their vaginal smears the next morning were regarded as pregnant and the day was designated as gestation day 0. Our preliminary study revealed that prenatal oral exposure to 100 μg/kg of PCB126 on gestational day 15 reduced neonatal body weight at birth. On the other hand, 30 μg/kg of PCB126 had no effect (6.9 ± 0.1 g [n = 6] vs 7.2 ± 0.3 g [n = 6], normal vs 30 μg/kg of PCB126, p = 0.3778). Thus, ten pregnant rats were treated orally with PCB126 at a dose of 30 μg/kg and the other ten pregnant rats with corn oil, its vehicle, on gestational day 15. All newborns were weighed on postnatal day 1 and each litter was reduced randomly to four males and four females. Only three females were born to one dam that exposed to corn oil although number of male offspring of the dam was nine. In this case, extra one male nursling of the litter was added so that the total number was eight. All female offspring were discarded at weaning. Male offspring were subjected to the present study at 4-5 weeks old. One animal from each litter was used for each behavioral test. Each animal experienced only one behavioral test. Thirty-six male offspring of rats with prenatal exposure to PCB126 and 36 male offspring with prenatal exposure to corn oil were used in the present study. The care and handling of the animals were in accordance with the "Azabu University Animal Experiment Guidelines; April 2000".

Rotating rod test

It was examined whether motor coordination of PCB126 rats was impaired using the rotating rod test. Rats were placed on a rotating rod (10 cm diameter,

Natsume, Tokyo) which was rotated at 3 rev./min for 10 min to habituate them to the apparatus. The next day, the rats were again placed on the rotating rod and the speed was increased in the order of 3, 5, 8, 10, and 15 rev./min every 1 min. The number of rats that successfully walked at each speed was recorded.

Locomotor activity and anxiety-related behavior in an open field

Locomotor activity was measured in a black wooden box (45 × 45 × 40 cm depth). The apparatus was located under concealed lighting which gave low luminance (55 lx). A rat was placed in the center of the box and left for 15 min. Its behavior was recorded by a digital video camera set above. The number of rearings and duration of grooming behavior, which are indices of anxiety (De Souza Spinosa et al. 1999; Moreira et al. 2000; Sonavane et al. 2002; Kalueff and Tuohimaa 2005), were measured by an observer blinded to the rats' history. The distance moved horizontally and the percent time spent in the 25 cm square in the center were measured using a computer-aided behavior analysis system (SMART, Bio Research Center, Aichi). The apparatus was cleaned using ethanol prior to each experiment.

Social interaction

Anxiogenic responses were measured utilizing a modified social interaction test (Sajdyk et al. 2002). A rat with prenatal exposure to either corn oil or PCB126 was put into an arena for the social interaction test (45 × 45 × 40 cm depth) with a novel partner rat of the same sex and of similar weight. Their behavior was video-recorded for 5 min with a digital video camera above. The time spent in social interaction (sniffing, following, grooming the partner, and wrestling) of the test animal provided a measure of anxiety. These measurements were performed by an observer blind to the rats' history.

Serum corticosterone level under non-stressful conditions and after forced swim stress

A Plexiglas cylinder (20 × 50 cm, diameter × height) filled with water (25°C) 30 cm in depth was used as a swim stress device. Each rat was put into the cylinder for 15 min and trunk blood was collected in a glass tube by decapitation immediately after forced swim stress. Rats were quickly removed from their home cage and trunk blood was collected as a non-stressful control. All blood collections were performed between 14:00–15:00. Serum corticosterone levels of trunk blood were measured using an RIA kit (Amersham, UK).

Statistical analyses

Results are expressed as the means ± S.E.M. or means + S.E.M. The effect of prenatal exposure to PCB126 was analyzed with unpaired *t*-test for body weight, locomotor activity and anxiety-related behavior in an open field, social interaction, and serum corticosterone level, and Fisher's exact probability test for the incidence of the rota-rod test. A p value < 0.05 was considered significant.

Results

Body weight

The body weights of male rats with prenatal exposure to corn oil and PCB126 on postnatal day 1 were 7.0 ± 0.1 g and 7.0 ± 0.1 g, respectively, with no statistical significance between the two groups.

Rotating rod test

The effect of prenatal exposure to PCB126 on motor coordination was examined using a rotating rod. At 3, 5, and 8 rpm, all rats accomplished the walking task (Table 1). At 10 and 15 rpm, 2–4 rats failed to accomplish the walking

Table 1. Effect of prenatal exposure to PCB126 (30 μg/kg, PO) or Corn oil on motor coordination in rotating rod test.

	Revolution (rpm)				
	3	5	8	10	15
Corn oil (n = 8)	8/8	8/8	8/8	6/8	4/8
PCB126 (n = 8)	8/8	8/8	8/8	8/8	5/8

Number of rats walking on the rotating rod for 1 min/Total number of rats is shown in the table.

task (Table 1); however, there was no difference between the two groups.

Locomotor activity and anxiety-related behavior in an open field

Total horizontal distance moved during 15 min in an open field was not affected by prenatal exposure to PCB126 (Fig. 1A). On the other hand, time spent in the center of the open field and the number of rearings fell (Fig. 1B and 1C), and total grooming duration was extended (Fig. 1D).

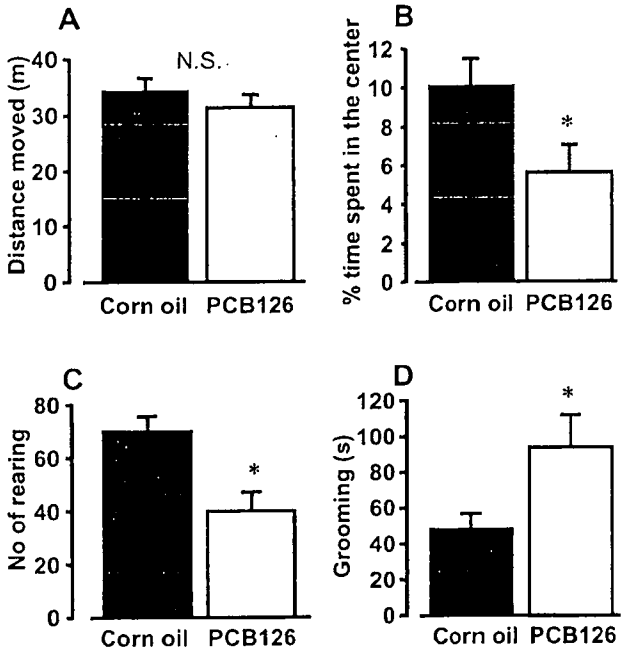

Fig. 1. Effect of prenatal exposure to PCB126 (30 μg/kg, PO) on behavioral parameters. Rats with prenatal exposure to corn oil or PCB126 were put into an open field for 15 min and locomotor activity (A), % time spent in the central area (B), number of rearings (C), and grooming duration (D) were measured. Data are presented as the mean + S.E.M. of 10 animals.
N.S., not significant. $^{*}p < 0.05$ vs corn oil, unpaired *t*-test.

Social interaction

Time spent in social interaction during the 5 min test period was 19.9 ± 2.6 s in rats with prenatal exposure to PCB126. This time was significantly shorter than that with prenatal exposure to corn oil, 32.5 ± 2.9 s (Fig. 2)

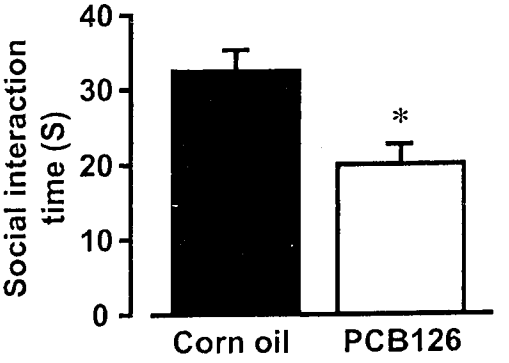

Fig. 2. Effect of prenatal exposure to PCB126 (30 μg/kg, PO) on social interaction. Rats with prenatal exposure to corn oil or PCB126 were put together with a novel partner rat and the time spent in social interaction (sniffing, following, grooming the partner, and wrestling) was measured. Data are presented as the mean + S.E.M. of 9 animals.
$^{*}p < 0.05$ vs corn oil, unpaired *t*-test.

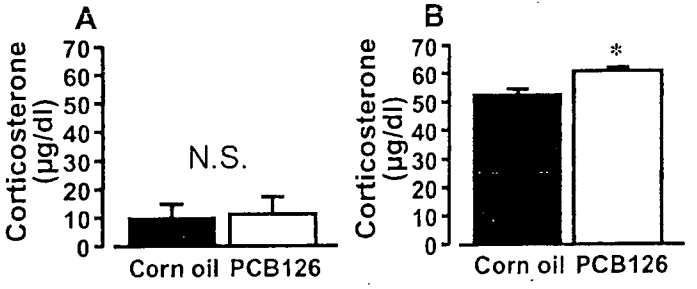

Fig. 3. Serum corticosterone level under non-stressful conditions (A) and after forced swimming (B) in rats with prenatal exposure to corn oil or PCB126. Data are presented as the mean + S.E.M. of 4 (A) and 5 (B) animals.
N.S., not significant. $^{*}p < 0.05$ vs corn oil, unpaired *t*-test.

Serum corticosterone level under non-stressful conditions and after forced swim stress

The serum corticosterone levels under non-stressful conditions were not affected by prenatal exposure to PCB126 (Fig. 3A); however, the increase in the serum corticosterone level induced by forced swim stress was significant (Fig. 3B).

Discussion

The present study revealed that open field performance was greatly influenced by prenatal exposure to PCB126. In rodents, grooming is particularly sensitive to stress and exogenous manipulation, and generally facilitated under stressful situations (Moyaho and Valencia 2002). In contrast, rearing, an exploratory behavior, is decreased under anxiogenic conditions as anxiogenic agents exerted a decrease in the number of rearings in an open field (De Souza Spinosa et al. 1999; Sonavane et al. 2002). Together with the evidence of decreased time spent in the center of the open field and decreased social interaction, which is a representative index of anxiety (Sajdyk et al. 2002), it is suggested that rats with prenatal exposure to PCB126 are sensitive to stress and have a propensity to develop anxiety.

Maternal stress exerted emotional disturbance, including anxiogenic behavior, through modification of the feedback mechanism of the offspring HPA (Henry et al. 1994; Patin et al. 2005). As the anxiogenic behavior of prenatally-stressed rats was abolished by maternal adrenalectomy, excess maternal corticosterone may cause this emotional disturbance (Zagron and Weinstock 2006). Literature data show that PCB has a property to elevate serum corticosterone when administered orally (De Krey et al. 1993; Miller et al. 1993), and the data of the present study show that prenatal exposure to PCB causes a disturbance of HPA response. It is conceivable from this evidence that the underlying mechanisms of the emotional disturbance induced by prenatal stress and PCB exposure may be common to both. Thus, dysfunction of the HPA axis may, at least in part, contribute to the emotional dysfunction of rats with prenatal exposure to PCB126. As hippocampal corticoid receptors decreased in prenatally-stressed rats (Henry et al. 1994), this mechanism may be involved in the dysfunction of HPA induced by prenatal exposure to PCB126. Further studies are necessary to prove this hypothesis.

To stay on the rotating rod, the rats required complex motor skills, including motor coordination and precise postural control. Nevertheless, prenatal PCB126 did not affect their performance, even at the highest rotation speed. Together with evidence that locomotor activity in an open field was not different in the two groups, prenatal PCB126 at the dose examined may not exert motor dysfunction, at least at the age subjected to the experiment. In previous studies, however, maternal exposure to PCB elicited motor dysfunction in the rotating rod test (Nguon et al. 2005) and swimming test (Pantaleoni et al. 1988). The former and latter studies administered Aroclor 1254 and Fenclor 42, respectively, both of which are commercial PCB mixtures. The dosing period was gestation day 11 through postnatal day 21, and gestation day 6 through 15, respectively. We administered PCB126 once on gestation day 15. The different types of PCB and dosing period may have caused the different effects on motor function.

The concentration of PCB126 in adipose tissue of Japanese was 120–730 pg/g (Kannan et al. 1989). When PCB126 was administered orally to rats at a daily dose of 10 μg/kg for 13 weeks, the concentration in adipose tissue was 645 ng/g (Van Birgelen et al. 1994). Thus, the amount of PCB126 in the adipose tissue of the present study is estimated to be about 1,000 times higher than that in humans. As the toxic effect is dependent on the dose, it is doubtful that PCB affects the central nervous system in humans. Indeed, there is little evidence available about the anxiogenic effect of prenatal exposure to PCB in humans; however, etiological study revealed that chronic inhalation of low chlorinated PCBs in school buildings was associated with increased emotional complaints in humans (Peper et al. 2005); therefore, we cannot reject the possibile effect of prenatal exposure to PCB126 on emotionality. Besides the toxicity of PCBs, additive or synergic neurodevelopmental effects of prenatal exposure

to PCBs and MeHg, which is also an environmental contaminant, have been evidenced in terms of motor dysfunction (Roegge and Schantz 2006) and toxicity to pituitary cells (Johansson et al. 2006). A cohort study of child development from the effects of perinatal methylmercury and environmental pollutants (Nakai et al. 2004) may uncover the intrinsic effect of prenatal exposure to PCB.

In summary, prenatal exposure to PCB126 decreased rearing and time spent in a central area, increased grooming in an open field, and decreased social interaction, although it did not affect total locomotor activity. This evidence suggests that rats with prenatal exposure to PCB126 are vulnerable to stress. As the serum corticosterone level increased in stressed rats with prenatal PCB126, dysfunction of the HPA axis may be one of the causes of anxiogenic properties.

Acknowledgments

The authors thank Drs. Kinji Shirota and Fumiaki Akahori for encouragement. This work was supported in part by the "High-Tech Research Center" Project for Private Universities: matching fund subsidy from the Ministry for Education, Culture, Sports, Science and Technology of Japan, 2002 –2006.

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