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Perinatal Brain Ischemia/Hypoxia As Progressive Capillary Bed Nonperfusion In A Context of Evolving Mitochondrial Excitotoxicity

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Abstract: Fundamental evolution of neuronal injury in terms of neural tissue alterations as developing in perinatal brain ischemia/hypoxia might underlie a variety of mechanisms implicating particularly a progressive form of nonperfusion of regional capillary bed blood flow. Indeed, a concept of immaturity of such regional capillary beds perfusion of the fetal/neonatal brain might help account for such progressiveness of nonperfusion that would render simple blood flow patterns of disturbance a primary mechanism in perinatal brain injury. In terms therefore of distinction between ischemia and hypoxia as arising from progressive nonperfusion of neural tissue capillary beds, one might perhaps realize systems of primary neuronal injury that would subsequently tend in certain cases to evolve in terms largely of suborganelle or mitochondrial injury. One might recognize primary and secondary order forms of neuronal and neural tissue injury in perinatal brain ischemia/hypoxia arising largely as progressive forms of nonperfusion of capillary beds that would operate essentially as degrees of such progressiveness towards further cellular and tissue injury.

Key words: Ischemia, hypoxia, mitochndril, capilly

INTRODUCTION

INTRA-UTERINE/PERINATAL ISCHEMIA/HYPOXIA AS LARGELY A PATHO-BIOLOGIC INSULT TO BRAIN DEVELOPMENT

A particularly distinct feature of prenatal and perinatal brain injury is the largely ischemic mechanism of injury infliction—that, in fact, the hypoxic element is in a peculiar way tied up with a major operative mechanism of ischemia. What are the precise characteristics of integral combination of hypoxia and ischemia in inducing brain damage around the time of birth?

Does ischemia in itself aggravate an accompanying hypoxic form of injury in purely hypoxic terms? In other words, discounting all the effects that a decreased blood supply to the brain would give rise to from placental blood flow (as in pre-eclampsia) or during the actual vaginal delivery of the infant, do in fact such periods of decreased blood supply to the infant brain in itself constitute the main operative mechanism in producing neuronal injury that is essentially mediated by decreased oxygen delivery or hypoxia?

In other words, can an impaired placental blood flow induce serious hypoxic neuronal injury to the infant brain in large measure as a main mechanism exerted by decreased cerebral blood flow? Alternatively, are the hypoxic effects on the infant and fetal brain simply a direct consequence of dynamic upsets of disturbed blood flow in the form of ischemia brought about by poor placental blood flow, as reflected in an upregulation of adrenomedullin gene expression in placenta and leukocytes?[1]. Or is it conceivable to consider a whole constellation of operative factors[2] responsible for abnormal brain development[3] as manifested for example clinically in cases of cerebral palsy or perinatal death, irrespective of an essential phenomenon of abnormal blood flow to the infant or fetal brain[4] or conversely apart from oxygen insufficiency independent to variable degree of dynamics of cerebral blood flow? In this sense, for example, a combined assessment of nucleated red blood cells and non-protein-bound iron might help identify high risk neonates[5], particularly in view of hemolysis as caused by severe hypoxia and acidosis[6].

The morphologic lesions classically described in such infants include hemorrhagic infarction, periventricular leukomalacia and telencephalic leukoencephalopathy[7].

The very diversity of these morphologic brain lesions in itself might indicate the highly diverse mechanisms whereby ischemic/hypoxic damage would be inflicted on the developing brain[8] in a full spectrum of variable expression of patterns of influence[9] ranging from effects of hypoxia to a full variety of abnormal patterns of blood

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flow independent to some extent of actual degree of hypoxia. This spectrum might include also oxidative stress in patterns of abnormal reperfusion of the cerebrum[10]. Also, proinflammatory cytokines produced by activated microglia would operate in a context of microcirculatory and metabolic effects in perinatal hypoxia/ischemia; also, Interleukin-10 would appear to markedly reduce such proinflammatory progression[11,12]. On the other hand Interleukin-18 would appear important for the development of hypoxic/ischemic brain injury in a context of microglial activation[13] and also of macrophage inflammatory protein-1 alpha expression[14].

It is for example conceivable that a rapidly developing brain in itself would be even more susceptible to ischemic/hypoxic injury due largely to factors specifically arising from dynamics of brain development[15]. Also, maturation-dependent vulnerability of oligodendrocyte progenitor cells to hypoxia-ischemia might underlie a predisposition for periventricular leukomalacia in the white matter of premature infants[16].

There would perhaps arise situations during intra-uterine life whereby, at particularly distinct stages of fetal brain development, a suboptimal delivery of oxygen would tend to render the brain especially susceptible to the effects of immediate ischemia/hypoxia and also to delayed forms[17] of such injury. Indeed, a rapidly developing and enlarging fetal brain would presumably demand progressively increasing amounts of oxygen as supplied to the organ with advancing gestation in a context that would at times fail to progress in terms of such oxygen availability.

Hence, probably, an essential aspect of intra-uterine ischemic/hypoxic injury is simply a failure to progressively render available more oxygen in terms of delivery to the developing fetal brain as pregnancy progresses. This would tend to affect also radial glial responsiveness as systems of neuritogenesis[18]. It is this phenomenon of failure to progressively increase oxygen availability in strict parallel correlation with rapid intra-uterine brain development as occurs in later stages of pregnancy that would essentially tend to underlie dynamics of ischemic/hypoxic injury to the fetus.

Added or superimposed on such an essential failure in oxygen availability would perhaps evolve a rapidly developing intrauterine series of events inherent to gestational maturation in brain development that subsequently induce a drop in blood supply to the fetal brain as seen in later stages of the pre-eclamptic pregnancy. Such a situation might develop perhaps during prolonged or difficult vaginal delivery whereby the fetus or infant is subjected to actual or absolute drops of cerebral blood supply during active labor. Such a situation would appear to involve a distinct series of events with consequences arising directly from functionally rapid development of the fetal brain as accentuated in later stages of gestation. However, it is still conceivable that delayed hypoxic or ischemic effects on subsequent postnatal development of the infant brain would constitute systems of progression arising from dynamics of absolutely decreased blood supply developing especially in later stages of pregnancy or during the actual period of vaginal delivery of the newborn[19].

Such degrees of complexity in pathogenesis as operative factors are responsible not only for inducing effect but also as systems capable of variable degrees of delayed progression in terms of ischemic/hypoxic injury to the fetal and newborn brain including white matter damage[20]. Production of reactive oxygen species by endothelial cells or of blood-borne factors would often operate in neuronal injury as induced by oxygen/glucose deprivation in neonates[21,22]. Within a contextual framework of the developing fetal and newborn brain, one might best interpret the whole phenomenon of perinatal ischemic/hypoxic brain damage simply as systems of stress inducing adapatations to a highly dynamic series of increasing requirements in terms of oxygen availability. As a function implicating cerebral/brain blood flow patterns, perinatal ischemia/hypoxia is influenced directly by mechanisms of maturation of a developing brain. In this regard, for example, color doppler ultrasonography would be prognostically valuable in neonates suffering from hypoxic/ischemic encephalopathy[23].

It is conceivable to consider delayed effects of brain damage to progressively become more severe as the brain not only increases in size but also matures as a function of previous exposures of effective brain ischemia/hypoxia. Episodes of ischemia/hypoxia in earlier parts of the pregnancy in damaging a fetal brain progressively develop since the actual dynamics and nature of development of the brain would transcend simple concepts of morphologic parenchymal or cellular damage as susceptible consequences of immediate hypoxia/ischemia in the perinatal period.

Hence, perhaps, there would develop essential adaptive change in response to ischemia/hypoxia during intra-uterine life whereby the postnatal brain constitutes in several ways a very immature organ with biologic characteristics that are primarily fetal. Indeed, hypoxia/ischemia would exert its main damaging effects especially on the actual developmental processes that are themselves responsible for roles of production of dynamic patterns of vascular blood flow and of responsiveness to decreased oxygen availability and effective utilization.

rather than on the fetal/newborn brain as simply a parenchymal organ.

Essential features of the fetal/newborn brain as a parenchymal organ and as a very immature organ still undergoing complex adaptations in responsiveness and as organizational and maturational[24] transformation would implicate intrauterine and perinatal ischemia/hypoxia that intrinsically arise and progress largely as defective oxygen availability and vascular blood flow disturbances. In this regard, endothelial nitric oxide would contribute towards maintenance of cerebral blood flow in combating neonatal hypoxia/ischemia[25].

Such a situation would clearly contribute towards rendering the intra-uterine and perinatal brain particularly susceptible to ischemia/hypoxia as manifested not only morphologically but especially in terms of actual functional[26] levels of the intellect and also as cerebral palsy.

INTEGRATION OF DISTURBED REGIONAL CAPILLARY BED BEYOND SIMPLE TARGET CELLULAR CONCEPTS OF INVOLVEMENT

Hypoxic-ischemic injury of the striatum in newborns might in a real way relate particularly to the distributional patterns of neuronal damage more as perfusion patterns of disturbed blood supply rather than specifically as selective vulnerability of neurons to such hypoxic/ischemic injury[27].

The concept itself of selective neuronal vulnerability to various forms of injury in cases of neonatal hypoxia/ischemia might actually derive from significant systems of pathogenesis that specifically induce abnormal dynamic parameters of blood flow to specific regions of the brain such as the basal ganglia and somatosensory systems in the neonatal brain.

Even more significant would be disturbances of blood flow not only on a patterned basis of evolving change but particularly in terms of specific parameters of oxygen delivery to the neurons.

A system of initial enhancement of hypoxic and of ischemic effects would perhaps tend to operate in perinatal brain damage, and it might perhaps be valid to consider a concept of defective oxygen delivery as related to specific regional groups of neurons to evolve not only as a progressive deterioration in blood flow per se but as capillary bed nonperfusion and impaired capillary wall diffusion.

Certain specific regional vascular beds are more susceptible to hypoxia/ischemia as an overall system of specific neuronal involvement; it might be true to consider such specific parameters of capillary bed perfusion to revolve essentially around progression of such neuronal injury as a regional tissue of pathologic involvement. In real terms, perhaps, injury to regional neural tissue rather than injury to individual neurons might operate in an overall system of progressive nonperfusion of specific regional capillary beds that especially progress to variable degree depending also on neural tissue parameters of initial damage.

In other words, phenomena such as edema of brain tissue[28] would constitute fundamental contributing factors towards progressiveness of hypoxic/ischemic injury of the neonatal brain in terms specifically arising from degrees of perfusion or of nonperfusion of the related regional capillary beds.

Systems of initial injury to brain tissue that in various ways prove progressive mainly as essential nonperfusion of regional groups of capillary beds would implicate a strict selectivity of neuronal and oligodendrocyte progenitor injury[29] as a regional phenomenon primarily delineated by capillary bed injury in the first instance.

It might be artificial to strictly consider pathogenesis of neuronal injury in hypoxic/ischemic brain damage as distinct from a whole series of pathogenetic pathways of progressive involvement of the related capillary beds that normally ensure oxygen availability. A fundamental aspect of neonatal/perinatal hypoxia/ischemia of the brain would directly implicate involvement primarily of brain tissue rather than of individual neurons or of individual groups of neurons; these would tend to transform particularly as disturbances of capillary perfusion with increased neural tissue injury.

In this context of perinatal hypoxia/ischemia, astrocyte-like cells that normally do not express endothelin-1 mRNA (ET-1mRNA) have showed an increased level of ET-1 mRNA; similarly, endothelial cells of capillaries and small vessels also express increased ET-1 mRNA in these cases[30].

EXCITOTOXICITY AS BASED ON TRANSFORMATION AT CELLULAR RECOVERY TOWARDS FULL PARTICIPATION OF THAT CELL IN INDUCING FURTHER CELLULAR INJURY

An essential aspect of neuronal or cellular excitotoxicity would appear to depend especially on aspects of the involved neuron or cell itself in a series of processes that dramatically lead to injury within a strict context of operative intracellular metabolic pathways[31]. Beyond a basic concept of excitatory forms of neuronal injury, phenomena of injury affect biologic mechanisms of

preservation of the neuron; this would implicate energy utilization by subcellular organelles as a likely basis for mitochondrial[32] participation towards the evolving progression of neuronal injury as a generic system of transforming injury[33].

In this regard, for example, production of excess glutamate as occurs with prolonged neonate seizure activity, would be especially toxic to neurons, particularly affecting the hippocampus[34]. Also, for example, endotoxin exposure of neurons would appear to significantly sensitize these cells to effects of hypoxia/ischemia[35].

Mitochondrial pathology would, in a generic sense, actually constitute in many cases an essential excitotoxic form of cellular injury as seen in several cell types including for example hepatocytes exposed to excess alcohol. In this regard, cyclooxygenase-2 might contribute to enhancing neonatal brain injury in perinatal hypoxia-ischemia, via different mechanisms that would include excitotoxicity and the production of reactive oxygen species[36]. In this sense, therefore, mitochondrial myopathies and neuropathies generally might not constitute a primary form of pathology but simply a secondary consequence with however a significant potential for progression in terms of excitotoxicity to which the myocyte or neuron would have been exposed to initially. Even the considerable variety of DNA mutations and deletions found in mitochondrial myopathies would in a sense perhaps be suggestive of a series of secondary damaging effects resulting from a full range of excitotoxic agents that would exert generic and also specific patterns of progressive damage.

The very concept of excitotoxicity coupled particularly with disturbances of ischemia/reperfusion phenomena would implicate the participation of oxygen-free radicals and nitric oxide derivatives, within contexts of inflammation that somehow tend to precipitate further progressiveness in neuronal injury. In this regard, also, compensatory systems of reperfusion and reoxygenenation after episodes of perinatal hypoxia/ischemia might induce abnormal blood flow patterns as via the vertebrobasilar arterial system[37].

It might be valid to consider an essential series of cellular biologic mechanisms[34] that participate in enhancing or in promoting a state of excitation on the part of biologic processes leading to neuronal/cellular recovery. However, such a state of excitation might constitute excitotoxic injury operating above a certain threshold of neuronal damage as developing specifically from previous exposure to ischemia or hypoxia.

In this sense, perhaps, the essential elicitation of excitatory responses on the part of the neuron or cell in an attempt towards recovery might actually have to be considered in the essential light of the presence of already existing damage/injury previously inflicted on that neuron or cell.

The excitotoxic injury itself perhaps should be recognized as a superimposition of damage to the cell or neuron that would derive much of its significance pathogenetically in terms largely of the nature of the initial lesion giving rise to a state of excititoxicity of potential progressiveness.

With ischemia, it is perhaps true that neurons often are already significantly injured due to a reperfusion deficit or to a reperfusion-associated series of injuries affecting groups of initially ischemic neurons. Basis for transformation of an essential excitatory attempt towards recovery resulting in essential excitotoxicity would perhaps paradoxically evolve simply as biologic mechanisms of neuronal maladaptation, as for example, in terms of mitochondrial injury. Excitotoxicity in an important sense would appear to involve potential cellular and subcellular organelle biologic processes that themselves would contribute actively to patterns of predetermined cellular recoverability. Also, for example, in pontosubicular neuronal necrosis, caspase-3 activation and caspase-like proteolytic activity would appear implicated in patterns of programmed neuronal cell death in perinatal brain hypoxia/ischemia[38].

CONCLUSIONS

Distinctive consequences of perinatal hypoxia and ischemia might actively induce neural tissue damage in terms of a vascularity that is inherently dynamic particularly with reference to a distinction between oxygen availability and oxygen utilization in a specific context of blood flow systems. Indeed, one might view the characteristics of perinatal brain damage as largely modes of involvement of neurons within subcompartments of progressive neural tissue injury as hypoxia evolves mainly in close relative fashion to dynamically disturbed blood flow rates in the brain.

Pperinatal brain damage is a particularly severe form of injury in terms of subsequent degrees of compromise of neural development as exerted by systems of impaired blood flow that specifically disturb oxygen availability not simply in quantitative terms but as effectively failed utilization of oxygen regionally.

One would view perinatal brain hypoxia/ischemia as evolving entirely within a single integral pathway of effective oxygen utilization by immature neural tissues; neurons lose their potential for both embryonic development and also their potential for viability in a

homeostatic setting of evolution from multipotential stem cell status to the endstage permanent cell status of the mature neuron with full differential potential in terms of functionality.

Perhaps systems of ischemia and of hypoxia in a setting of a difficult vaginal delivery might actually relate particularly to modes of influence of disturbed placental blood flow that would drastically transform fetal cerebral blood flow dynamics to a failed system of effective oxygen utilization by neural tissue. This would constitute primarily a vascular network beyond simple considerations of just a neuronal field of vascular supply. One might paradoxically view the primary target of injury in perinatal brain hypoxia/ischemia as the supplying capillary vascular bed in a manner arising directly from how ischemia adversely influences effective oxygen utilization by regional tissues rather than just by individual cells. Perinatal brain ischemia/hypoxia would constitute a tissue injury that transcends cellular concepts of transforming damage.

Indeed, the cerebral capillary bed would primarily result in a set of pathways of progressive pathology that would definitively dictate patterns of brain tissue injury in distinctively determining clinical outcome in terms of developmental and viability attributes of whole tissue regions.

Somehow, a system of hypoxic brain injury would constitute patterns of neuronal injury in terms of how any associated ischemia to tissues concerned would evolve via various pathways of progressive involvement. In a real sense, individual neuronal susceptibility to such an integrated hypoxic and ischemic effect would summate as a single injury incorporated within tissue response patterns of attempted recovery from such injury. A basic concept of cellular hypoxic/ischemic injury would in various ways have to account for integral tissue participation as seen in so many cases of perinatal brain injury that evolve as effective progression of cerebral palsy.

It is precisely this essential paradox of an actual neuronal form of hypoxic/ischemic injury that begins and progresses apparently as a primary tissue pattern of involvement that would especially characterize perinatal brain injury in terms of a hypoxia and ischemia of compounding effect.

Ischemia would appear to ensure progressiveness of hypoxic cellular injury that would transform to integral tissue progressiveness largely responsible for the clinical evolution and establishment of many cases of cerebral palsy.

A simplistic view of just hypoxia as the central mechanism inducing perinatal injury to brain tissue and to neurons would effectively fail to account for a patterned series of pathway effects evolving largely as capillary bed insufficiency as reflected for example in the hemorrhagic lesions often identified in fetal brains exposed to perinatal hypoxia/ischemia.

REFERENCES

1. Trollmann, R., E. Schoof, E. Beinder, D. Wenzel, W. Rascher and J. Dotsch, 2002. Adrenomedullin gene expression in human placental tissue and leukocytes: A potential marker of severe tissue hypoxia in neonates with birth asphyxia. Eur. J. Endocrinol., 147: 711-716.
2. Froen, J.F., G. Americo, B. Stray-Pedersen and O.D. Saugstad, 2002. Determinental effects of nicotine and andotoxin in the newborn piglet brain during severe hypoxemia. Biol. Neonate., 82: 188-196.
3. Geddes, R., R.C. Vannucci and S.J. Vannucci, 2001. Delayed cerebral atrophy following moderate hypoxia-ischemia in the immature rat. Dev. Neurosci., 23: 180-185.
4. Vescler, Z.S. and D.M. Ferriero, 2001. Molecular and biochemical mechanisms of perinatal brain injury. Semin Neonatol., 6: 99-108.
5. Perrone, S., R. Bracci and G. Buonocore, 2002. New biomarkers of fetal-neonatal hypoxic stress. Acta Paediatr. Suppl., 91: 135-138.
6. Bracci, R., S. Perrone and G. Buonocore, 2002. Oxidant injury in neonatal erythrocytes during the perinatal period. Acta Paediatr. Suppl., 91: 130-134.
7. Grafe, M.R. and H.C. Kinney, 2002. Neuropathology associated with stillbirth. Semin Perinatol., 26: 83-88.
8. Sunshine, P., 2002. Hypoxic-ischemic encephalopathy: Pathophysiology and implications for therapy. Przegl. Lek., 1: 6-9.
9. Evrard, P., 2001. Pathophysiology of perinatal brain damage. Dev. Neurosci., 23: 171-174.
10. Jensen, F.E., 2002. The role of glutamate receptor maturation in perinatal seizures and brain injury. Intl. J. Dev. Neurosci., 20: 339-347.
10. Levy, R., S. Glozman, D. Milman and C. Seruty *et al.*, 2002. Ischemic reperfusion braininjury in fetal transgenic mice with elevateed levels of copper-zinc superoxide dismutase. J. Perinat. Med., 30: 158-165.
11. Mesples, B., F. Plaisant and P. Gressens, 2003. Effects of interleukin-10 on neonatal excitotoxic brain lesions in mice. Brain Res. Dev. Brain Res., 141: 25-32.
12. Froen, J.F., B.H. Munkeby, B. Stray-Pedersen and O.D. Saugstad, 2002. Interleukin-10 reverses acute detrimenatl effects of endotoxin-induced inflammation on perinatal cerebral hypoxia-ischemia. Brain Res., 942: 87-94.
13. Hedtajru, M., A.L. Leverin, K. Eriksson, K. Blomgreu, C. Mallard and H. Hagber, 2002. Interleukin-18 involvement in hypoxic-ischemic brain injury. J. Neurosci., 22: 5910-5919.

14. Cowell, R.M., H. Xu, J.M. Galasso and F.S. Silverstein, 2002. Hypoxic-ischemic injury induces macrophage inflammatory protein-1 alpha expression in immature rat. Brain Stroke, 33: 795-801.
15. Ness, J.K., M.J. Romanko, R.P. Rothstein, T.L. Wood and S.W. Levison, 2001. Perinatal hypoxia-ischemia induces apoptotic and excitotoxic death of periventricular white matter oligodendrocyte progenitors. Dev. Neruosci., 23: 203-208.
16. Back, S.A., B.H. Han, N.L. Luo and C.A. Chricton *et al.*, 2002. Selective vulnerability of late oligodendrocyte progenitors to hypoxia-ischemia. J. Neurosci., 22: 455-463.
17. Du Plessis, A.J. and J.J. Volpe, 2002. Perinatal brain injury in the preterm and term newborn. Curr. Opin. Neurol., 15: 151-157.
18. Ganat, Y., S. Soni, M. Charon, M.T. Schwartz and F.M. Vaccarino, 2002. Chronic hypoxia up-regulates fibroblast growth factor ligands in the perinatal brain and induces fibroblast growth factor-responsive radial glial cells in the sub-ependymal zone. Neuroscience, 112: 977-991.
20. Hogberg, H., D. Peebles and C. Mallard, 2002. Models of white matter injury: Comparison of Infectous Hypoxic-Ischemic, or Exertotoxic Insults Ment Retard. Dev. Disabil. Res. Rev., 8: 30-38.
21. Peeters-Scholte, C., J. Koster and W. Veldheus *et al.*, 2002. Neuroprotection by selective nitric oxide synthase inhibition at 24 hrs after perinatal hypoxia-ischemia stroke, 33: 2304-2310.
22. Martin, L.J., 2000. Neuronal death in newborn striatum after hypoxia-ischemia is necrosis and evolves with oxidative stress. Neurol. Dis., 7: 169-191.
22. Peeters, C., D. Hollen, F. Groenendaal, F. Van Bel and D. Bar, 2003. Deferoxamine, allopurinol and oxypurinol are not neuroportective after oxygen/glucose deprivation in an organotypic hippocampal model, lacking functional endothelial cells. Brain Res., 963: 72-80.
23. Kirimi, E., O. Tuncar, B. Atas, M.E. Sakarya and A. Ceylan, 2000. Clinical value of color doppler ultrasonography measurements of full-terms neonates with perinatal asphyxia and hypoxic ischemic encephalopathy in the first 12 hours of life and long terms prognosis Tohoku. J. Exp. Med., 197: 27-33.
25. Nakata, M., K. Anno, N. Sugino, L.T. Matsumori, Y. Nakamura and H. Kato, 2002. Effect of intrauterine ischemia-hypoxia on endothelial nitric oxide synthase in fetal brain in rats. Biol. Neonate., 82: 117-121.
26. Aden, U., V. Dahlberg, B.B. Fredholm, L.J. Lai, Z. Chen and B. Bjelke, 2002. MRI evaluation and functional assessement of brain injury after hypoxic ischemia inneonatal mice stroke, 33: 1405-1410.
27. Martin, L.J., 2000. Neuronal death in newborn striatum after hypoxia-ischemia is necrosis and evolves with oxidative stress. Neurnol. Dis. 7: 169-191.
28. Lingwood, B.E., K.R. Dunster, P.B. Colditz, L.C. Ward, 2002. Noninvasive measurement of cerebral bioimpendence for detection of cerebral edema in the neonatal piglet. Brain Res., 945: 97-105.
29. Levison, S.W., R.P. Rothstein, M.J. Romanko, M.J. Snyder , R.L. Meyers and S.J. Vannucci, 2001. Hypoxia/ischemia depletes the rat perinatal subventricular zone of oligodendrocyte peorgenitors and neural stem cells. Dev. Neurosci, 23: 234-247.
30. Tsang, M.C., A.C. Lo, P.T. Cheung, S.S. Chung and S.K. Chung, 2001. Perinatal hypoxia-ischemia-induced endothelin-1 mRNA in astrocyte-like and endothelial cells Neuroreport, 12: 2265-2270.
31. Fukamachi, S., A. Furuta, T. Ikeda and T. Ikenoue *et al.*, 2001. Altered expressions of glutamate transporter subtypes in rat model of neonatal cerebral hypoxia and ischemia. Brain Res. Dev. Brain Res., 132: 131-139.
32. Puka-Sundvall, M., E. Gilland and H. Hagberg, 2001. Cerebral hypoxia-ischemia in immature rats: Involvement of mitochondrial permeability transition. Dev. Neurosci. 23: 192-197.
33. Lea, P.M. and A.L. Fadem, 2001. Traumatic brain injury: Developmental Differences in Glutamate Receptor Response and the Impact on Treatment ment Retard Dev. Disabil. Res. Rev., 7: 235-248.
34. Yager, J.Y., E.A. Armstrong, H. Miyashita and E.C. Wirrell, 2002. Prlonged neonatal seizures exacerbate hypoxic-ischmeic brain damage: Correlation with Cerebral Energy Metabolism and Excitatory Amino Acid Release Dev. Neurosci., 24: 367-381.
35. Coumans, A.B., J. Middelanis, Y. Garnier and H.M. Vaihinger *et al.*, 2003. Intracisternal application of Endotoxin Enhances the susceptibility to subsequent hypoxic-ischemic brain damage in neonatal rats. Pediatr. Res., (epub ahead of print).
36. Toti, P., D.E.C. Felice, K. Shurfeld and M. Stumpo *et al.*, 2001. Cyclo-oxygenase-2 immunoreactivity in the ischemic neonatatal human brain. An autopsy study. J. Submicrosc Cytol. Pathol., 33: 245-249.
37. Ioroi, T., C. Peeters-Schulte, I. Post, C. Leusink, F. Groenendaal and F. Van Bel, 2002. Changes in cerebral hemodynamics, regional oxygen saturation and amplitude-integrated continuous EEG during hypoxia-ischemia and reperfusion in newborn piglets. Exp. Brain Res., 144: 172-177.
38. Rossiter, J.P., L.L. Anderson, F. Yang and G.M. Cole, 2002. Caspase-3 activation and caspase-like proteo9lytic activity in human perinatal hypoxic-ischemic brain injury Acta. Neuropathol (Berl), 103: 66-73.