Regional Cerebral Blood Flow in Schizophrenia and the Local Circuit Neurons Hypothesis

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Abstract

It has been suggested that nitric oxide, a nonconventional intracellular and intercellular messenger involved in various biological and nervous system functions, may play a crucial role in a sophisticated cerebral microvascular system that regulates cerebral blood flow (CBF) under resting and activated conditions. A review of regional cerebral blood flow (rCBF) studies in schizophrenia shows that in schizophrenia patients this microvascular regulatory system may be deficient, failing to selectively raise rCBF in areas of the frontal and temporal lobes to respond to the physiological load placed on brain cells in these areas during certain neuropsychological tasks. A hypothesis about the more general role of local circuit neurons (LCNs) in the pathophysiology of schizophrenia is revised in light of recent information about both the characterization of LCN subpopulations and the interactions of multiple neurotransmitter systems in midbrain, striatum, and cortex. This revision helps explain the subtle rCBF regulatory failure, as well as other failures in information processing, in schizophrenia patients and points to interneurons as likely sites for the action of both typical and atypical antipsychotic drugs.


Although several powerful vasodilators, including hydrogen ions and carbon dioxide (CO₂), potassium ions, oxygen, some neurotransmitters, adenosine, and, recently, nitric oxide, have been suggested as the main agent in regulating cerebral microcirculation during neural activity, the mediator responsible for connecting cerebral blood flow (CBF) to brain activity has still not been identified (Iadecola 1993). It is clear, however, that there is a sophisticated cerebral microvascular regulatory system that provides almost instantaneous delivery of the nutrients and oxygen necessary to satisfy the constantly changing metabolic needs of brain cells. These nutrients are supplied with such topographic precision that one branch from a pial artery can be dilated and perfusing neurons engaged in an activity while neighboring columnar patterns of cells not participating in this neural activity but supplied by another branch of the same parent pial artery remain minimally perfused (Ngai et al. 1988).

Despite the often grossly disturbed behavior of individuals diagnosed with schizophrenia, the underlying neuropsychiatric disorder is notorious for only subtly disrupting higher integrative and cognitive functions. This subtle disruption suggests that subtle brain changes are responsible for disordered functioning, so it is not surprising that the cerebral microvascular regulatory system figures prominently among the suspected culprits. Measuring regional cerebral blood flow (rCBF) has thus become an important part of the...
current discussion on the neural basis of schizophrenia.

rCBF Regulation

It is widely believed that, in the absence of a major disruption in cerebral autoregulation, CBF is determined mainly by neuronal activity and metabolism (Roy and Sherrington 1890). Under normal conditions and in the steady state, there is close coupling between rCBF, local cerebral metabolic rates for glucose, and regional cerebral metabolic rates for oxygen (Raichle et al. 1976; Roland 1984), even though departures from steady state are associated with striking reversals of this correlation (Fox and Raichle 1986). In general, gray cerebral matter has a much faster metabolism and blood flow than white matter. Metabolically speaking, axonal terminals—where neurotransmitters are synthesized and released—seem to be the most active parts of neurons (Mata et al. 1980). The local vascular response in the immediate vicinity of the active neurons has recently received much research attention, but it is the coordinated regulation of the local microcirculation and upstream resistance vessels, the pial arteries, that has been difficult to account for in hypotheses that suggest various substances as vasodilators (e.g., CO₂, nitric oxide, certain neurotransmitters, and adenosine).

One such hypothesis, the nitric oxide hypothesis, proposes that, among other aspects of nitric oxide’s impact on biological processes (Moncada and Higgs 1993) and nervous system functions (Schmidt and Walter 1994), the synaptic activity-driven Ca²⁺/calmodulin-dependent synthesis and subsequent diffusion of nitric oxide may be critically important for the control of rCBF (Gally et al. 1990; Bredt et al. 1991; Iadecola 1993; Iadecola et al. 1994). Nitric oxide, being diffusible, is believed to alter the synaptic efficacy of both its synapses of origin and the synapses in the surrounding neural space, and to reflect the synaptic activity of each local region of neuropil. It is thought to control rCBF by guanylyl cyclase activation-mediated and/or potassium (K⁺) channel activation-mediated hyperpolarization of smooth muscle cells. This hyperpolarization leads to voltage-dependent calcium (Ca²⁺) channel closure and cytosolic Ca²⁺ reduction and storage in intracellular compartments and, ultimately, to relaxation of the smooth muscle cell lining of intracerebral arterioles and of the contractile pericytes of cerebral capillaries (Iadecola 1993). In both rats and primates nitric oxide synthase (NOS), the enzyme synthesizing the nitric oxide, is colocalized in the same neuronal populations as nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d), the enzyme facilitating the electron transport of biological oxidative processes. One aspect of these NOS/NADPH-d-positive neurons makes them particularly interesting: NADPH-d may protect nitric oxide-producing cells from the effects of nitric oxide released under neurotoxic conditions (Bredt et al. 1991). NADPH-d neurons in the neocortex may thus be resistant to neurodegenerative effects and could therefore be useful in studying potential neurodevelopmental disturbances in the human brain (Akbarian et al. 1993a, 1993b). NOS is localized in neurons, endothelial cells, and macrophages and, with NADPH-d, occurs in at least one subset of the nonpyramidal interneuronal class—the persistent and low-threshold spike interneurons (Kubota et al. 1993) characterized and discussed below. NOS/NADPH-d-positive interneurons also seem to colocalize somatostatin, neuropeptide Y, and some Ca-binding proteins such as calbindin and have been reported to contain the enzyme that synthesizes gamma-aminobutyric acid (GABA) (Hendry et al. 1984; Bredt et al. 1991; Akbarian et al. 1993a, 1993b). Ultrastructural studies have shown that NOS/NADPH-d neurons, in spite of their relatively small total number, produce extensive ramifications in the neocortex, forming a dense network with dendrites and axons closely opposed to intracerebral arterioles and capillaries (Iadecola 1993). Considering the characteristics of the NOS/NADPH-d-positive neurons, it would be intriguing, to say the least, to see if they can be more specifically implicated in the patterns of pathophysiology emerging from studies on rCBF in schizophrenia.

Selective Review of rCBF Studies in Schizophrenia

Following Kety and Schmidt’s pioneering studies of whole-brain blood flow using the nitrous oxide inhalation technique (Kety and Schmidt 1948), the quantitative determination of CBF went through several developmental stages (intracarotid ¹³³Xenon [¹³³Xe] and ¹³³Xe inhalation two-dimensional techniques) before culminating in three-dimensional single photon emission computed tomography
odologies is always problematic, Devous 1989; Holcomb et al. 1989). Tomography (PET) (Lassen and (SPECT) and positron emission tomography (PET) (Lassen and Ingvar 1972; Obrist et al. 1975; Devous 1989; Holcomb et al. 1989). While comparing the results of studies using different methodologies is always problematic, the risk may be worth taking if the specificities and limitations of each method and the potential confounding issues are kept in mind. For instance, the intracarotid $^{133}$Xe method produces unilateral data on only one hemisphere. The $^{133}$Xe inhalation method is able to tap only the cortical rim flow, which is somewhat underestimated. When a retained type of flow tracer such as the $^{99m}$Tc-HMPAO compound is used in SPECT in highly perfused regions, there is also a higher degree of tracer backflux out of the brain cells, so an activation-induced rCBF increase will be underestimated. Using oxygen ($^{15}$O)-labeled water, PET can measure blood flow easily, accurately, and safely, with the possibility of multiple measurements during the same session. Major confounding issues such as heterogeneity of patients and selection of control subjects, gender (women have higher flows than men), medication intake, scanning conditions (resting vs. nonspecific and specific activation), tracer characteristics, camera resolution, image analysis strategy, and methodological advancements should also be addressed. For example, recent developments in PET (SPECT is on the threshold of this capability) have given it the capacity to measure subtle changes of rCBF in discrete, progressively smaller cerebral structures through neuroanatomical-functional coregistration and image merging (Evans et al. 1988, 1992), exploitation of modern activation–rest subtraction paradigms (Weinberger et al. 1986; Fox et al. 1988; Friston et al. 1989, 1990), and pixel-by-pixel and voxel-by-voxel correlational approaches (Bench et al. 1990; Andreasen et al. 1992; Roland et al. 1993).

**Hypofrontality and rCBF Studies.**

Ingvar and Franzen (1974; Franzen and Ingvar 1975a, 1975b) were the first to call attention to the failure of medicated chronic schizophrenia patients to manifest the typical “hyperfrontal” pattern of rCBF seen in normal individuals following cognitive activation. They also noted that the more withdrawn and autistic the patient, the lower the flows shown in the frontal areas, while the more positive symptoms a patient had, the higher the flows displayed in postcentral and temporal areas (Ingvar and Franzen 1974; Franzen and Ingvar 1975a, 1975b). The fact that the patients studied continued to take their routine psychopharmacological medication raised the possibility that neuroleptics might have been responsible for the lower flows in frontal areas.

Early $^{133}$Xe intracarotid studies showing hypofrontality and a reduced anteroposterior CBF gradient were subsequently replicated by $^{133}$Xe inhalation studies (Geraud et al. 1987; Mathew et al. 1988; Mathew and Wilson 1990). Although the chronicity was considered responsible for the hypofrontality in some of these studies (Mathew and Wilson 1990), its reversal to “near-normal frontality” (Geraud et al. 1987) focused attention on other confounding factors, such as long-term treatment and severity of negative symptoms (for a review see Andreasen et al. 1992, table 1).

Another series of carefully designed $^{133}$Xe inhalation studies demonstrated that the hypofrontality became even more pronounced during activation by the Wisconsin Card Sorting Test (WCST; Milner 1963) and could be localized to the dorsolateral prefrontal cortex (DLPFC) (Berman et al. 1986; Weinberger et al. 1986, 1988; Raes et al. 1989). Including cognitive activation in the research design permitted each subject to be used as his or her own control and allowed the hypofrontality to be redefined as the inability to increase frontal flow in response to a frontal lobe stimulus. Weinberger et al. interpreted the failure of neuropsychological tests to activate the DLPFC in either medicated or medication-free patients as a stable trait of schizophrenia that reflected impaired neuronal metabolism in DLPFC. These results were reinforced by PET metabolic studies (for reviews, see Bachneff 1991, table 1; Andreasen et al. 1992, table 2) as well as by some recent SPECT rCBF $^{99m}$Tc-HMPAO studies (Rubin et al. 1991; Lewis et al. 1992; Steinberg et al. 1992), even though the $^{99m}$Tc-HMPAO method may have underestimated the activation-induced rCBF values. However, a substantial number of rCBF (Mathew et al. 1982; Gur et al. 1983, 1985, 1989), PET metabolic (glucose and $^{15}$O), PET rCBF ($H_2^{15}$O), and SPECT rCBF studies could not find hypofrontality (for reviews, see Bachneff 1991, table 2; Andreasen et al. 1992; see also Sheppard et al. 1983; Early et al. 1987; Bajc et al. 1989). These discrepancies suggest that comparing flow, metabolic, and PET and
SPECT studies may be problematic. Six recent studies, five rCBF (two cortical probe and three SPECT) and one metabolic PET (Wolklin et al. 1992), have increased interest in the hypofrontality hypothesis of schizophrenia. One of the cortical probe studies (Berman et al. 1993) found suggest that long-term neuroleptic very similar to those for normal but tended, on the contrary, to be history of greater neuroleptic in- cant differences in rCBF in the discordant pairs the twin with the prefrontal cortex (PFC) of the af- discordant pairs were found only during the WCST and only in the affected twin. Moreover, in the con- cordant pairs the twin with the history of greater neuroleptic in- take was not the more hypofrontal but tended, on the contrary, to be the more hyperfrontal of the pair. The rCBF values for the unaffected twin in the discordant pairs were very similar to those for normal discordant pairs. The results of the study emphasize that the PFC is the only cortical area in which the affected twin can be distin- guished from the well twin and suggest that long-term neuroleptic treatment is not a major factor in prefrontal dysfunction in schizo- phrenia. The number of the twin pairs investigated, however, was small. The other cortical probe study (Berman et al. 1993) found that depressed patients, unlike those with schizophrenia, were able to raise their rCBF in PFC under the WCST. This observation does not bear out an earlier con- tention that prefrontal hypofunc- tion is a nonspecific pathophysio- logical mechanism common to both depression and schizophrenia.

One of the three SPECT studies (Andreasen et al. 1992) showed that with appropriately challenged schizophrenia patients hypofrontality was displayed most prominently not only in drug-free but also in never-medicated first-episode patients, especially those showing negative symptoms. The hemispheric CBF of all three groups (controls and drug-free and drug-naive patients with schizo- phrenia) increased bilaterally under the activating condition, however. This suggests that inability to select- ively raise rCBF in a brain area such as the PFC in the face of an intact capacity to generally increase hemispheric or whole-brain CBF (but see Gur et al. 1994) could be related to a hypo(dys)function of the microcirculatory regulatory sys- tem discussed above. Such a distur- bance might involve regional deficiencies in those nitric oxide- producing NOS/NADPH-d intrinsic PFC neurons recently suggested as being a critical, though not the only important, factor for rCBF regulation (Iadecola 1993) or in other subpopulations of intrinsic nonpyramidal neurons that have recently been shown to have a re- duced density in schizophrenia pa- tients (Benes et al. 1991; but for contradictory results see Bunney et al. 1993; Daviss and Lewis 1993; Selemon et al. 1993) and which are also GABAergic (peptidergic) but more vulnerable than NOS/ NADPH-d cells to neurotoxic re- lease of nitric oxide by their nitric oxide-producing neighbors. Interesting inferences can be drawn when the other two SPECT rCBF studies are compared. One study (Ebmeier et al. 1993), done “at rest” on actively psychotic unmedicated patients using an HMPAO tracer but without cogni- tive or other controlled neuropsy- chological activation tasks, demon- strated a hyperfrontal pattern in superior right PFC and a hypoper- fusion in anterior cingulate bilat- erally and in the left temporal cort- ex. The other SPECT rCBF study (Paulman et al. 1990), performed with the help of a WCST activation procedure on chronic patients (half of them medicated and the other half unmedicated), showed significant bifrontal and bitemporal cortical flow deficits within the context of significantly elevated hemispheric blood flow in patients when compared with controls. This again suggests that schizophrenia patients may resort to activating larger (e.g., hemispheric) brain vol- umes to compensate for their ap- parent inability to raise rCBF in discrete areas, such as PFC, that would have been both more app- propriate and sufficient for the task at hand.

In summary, it appears that failure to increase neural activity, metabolism, and blood flow in specific brain areas such as the PFC (dorsolateral, mesial, etc.) and temporal cortex, after the influ- ences of general, probably arousal- related, increases of neural activity and flow on these areas have been eliminated, represents a stable trait of schizophrenia. This trait may stem, at least in part, from the under- lying pathophysiology of the ill- ness and can be found independ- endently of medication status and chronicity in most if not all stud- ies where a controlled activation procedure has been carried out (Berman et al. 1986; Weinberger et al. 1986; Raese et al. 1989; Rubin et al. 1991; Andreasen et al. 1992). The “hypofrontality issue” in schizophrenia might never have turned into a “literature conflict” between medicated and unmedi- cated patients or acute versus chronic states had the testing been
performed under an appropriate activating condition that placed a normal physiological load on the tested brain area to uncover latent or subtle abnormalities under stress. The affected brain area need not be neuroanatomically predetermined in the sense of coinciding with a rigidly defined region of interest but could be a neurophysiologically flexible task-related composite of the smallest identifiable task-activated areas and volumes corresponding to the pixels and voxels involved. Traditional regions of interest could hardly be a proper topographic reflection (Bench et al. 1990) of the task-activated and distributed neuronal systems that are dynamically constituted and recruited out of a pool of functional neuronal networks. Examples of some of the most important current methodological problems and developments are (1) the relationship between global and local CBF changes that necessitates use of an adequate normalization procedure (Friston et al. 1990) to compute relative CBF values and (2) automated methods of edge detection and identification of intrinsic brain landmarks directly from PET or SPECT images (Minoshima et al. 1993) that are then realigned and registered into the standard stereotactic space (Talairach and Tournoux 1988) for precise neuroanatomical localization.

Hemispheric Laterality and rCBF Studies. For some time, evidence of left hemispheric dysfunction in schizophrenia (Gur 1978) has been growing out of neuropsychology studies (Wexler 1980) that showed deficient functioning of the left hemisphere in schizophrenic patients and a paradoxical heavier reliance on the deficient left hemispheres during performance of tasks more appropriately executed by the right hemisphere (Gur 1979; Flor-Henri 1983). Subsequent rCBF studies showed that control subjects at rest had left-sided rCBF higher than right in inferior frontal and DLPFC and had right rCBF higher than left in parietal and occipital regions (Lewis et al. 1992) and were able to differentially increase hemispheric blood flows on the left or the right depending on whether they were performing verbal or spatial tasks. But medicated schizophrenia patients showed no flow asymmetry for verbal tasks and greater left hemispheric increase for spatial tasks (Gur et al. 1983). Unmedicated schizophrenia patients at rest also had higher left hemispheric flows, particularly in anterior regions (Gur et al. 1985). Treatment reestablished symmetry in CBF, leading the authors to conclude that neuroleptics restore symmetry of resting flows before producing symptomatic relief. In a similar vein it has been concluded (Rubin et al. 1991) that while medication affected prefrontal rCBF and metabolism, these changes occurred before any treatment effects.

Some PET metabolic studies (Buchbaum et al. 1982; Brodie et al. 1984; Wolkin et al. 1985) also found evidence for left hemispheric dysfunction, expressed as left hypofrontality in schizophrenia. But many more PET studies either did not test or could not find asymmetric flows (for reviews, see Bachner 1991, tables 1 and 2, and Andreasen et al. 1992). In summary, although deficits of flow and metabolism activation on the left side (Paulman et al. 1990; Rubin et al. 1991; Andreasen et al. 1992; Lewis et al. 1992; Gur et al. 1994) seem to predominate (but see Wolkin et al. 1992), hemispheric laterality studies have either been inconsistent, lacked sufficient statistical power to be conclusive, or allowed the laterality issue to be overshadowed by the issue of more discretely localized rCBF patterns of pathology (Liddle et al. 1992; Ebmeier et al. 1993).

Relationships of Neuropsychologically Defined Symptoms and Syndromes With Regional Hypoperfusion Patterns in Schizophrenia. The first reports of inverse correlations between negative symptoms of schizophrenia and frontal cortical flows and of positive correlations between positive symptoms and postcentral and temporal blood flows (Ingvar and Franzen 1974) were provocative. Later rCBF SPECT (Andreasen et al. 1992) and metabolic PET studies (Wolkin et al. 1992) replicated this relationship either partially (Volkow et al. 1987; Wiesel et al. 1987; Bajc et al. 1989; Lewis et al. 1992) or fully (Rubin et al. 1994). Other studies demonstrated hyperperfusion in the left temporal cortex (Mathew et al. 1998) in association with auditory hallucinations (McGuire and Murray 1992), higher left/right frontal perfusion ratio correlation with increased anergia on the Brief Psychiatric Rating Scale (Overall and Gorham 1962) (Baker et al. 1992), and inability of patients to activate inferior PFC rCBF bilaterally and to suppress left striatal rCBF (Rubin et al. 1991). Recent increases in the resolution power of SPECT and PET cameras below 10 mm (Berman et al. 1991) have produced even more topographically specific results. A
SPECT $^{99m}$Tc-HMPAO study found an increased rCBF in left posterior (superior temporal and occipital) cortical areas, caudate, and thalamus in chronic medicated outpatients, as well as decreased rCBF in left frontal (mesial, inferior, and DLPFC) cortical regions, with negative symptoms correlating inversely with mesial frontal rCBF, particularly on the left (Lewis et al. 1992).

A recent PET ($^{15}$O$_2$) study showed specific hypo- and hyper-perfusion patterns that could be used to distinguish between three factor-analysis-derived syndromes in chronic schizophrenia patients maintained on antipsychotic medication (Liddle and Barnes 1990; Liddle et al. 1992). The first syndrome—increased psychomotor poverty—correlated with decreased rCBF in left DLPFC (Brodmann’s area [BA] 46), left medial PFC (BA 10), and left anterior cingulate (BA 24, 32), as well as with increased rCBF in both caudate heads, or, on the authors’ hypothesis, with impairment in the self-directed generation of mental activity, that is, with hypo(dys)functional left DLPFC and limbic cortex and hyperfunctional caudate nuclei. The second syndrome—increased disorganization—correlated with decreased rCBF in right ventral PFC (BA 47, 45) and in left Broca’s area (BA 44) and with increased rCBF in right anterior cingulate (BA 24, 32) and right medial PFC (BA 9, 10), or, as interpreted by the authors, with impaired ability to suppress intrusion of irrelevant mental activity, that is, with hypo(dys)functional right ventral PFC and hyperfunctional right limbic cortex. Finally, increased reality distortion correlated with decreased rCBF in right caudate and right posterior cingulate and with increased rCBF in left parahippocampal (BA 27, 30), left superior temporal pole (BA 22), left ventral striatum, and left DLPFC, or, according to the authors, with less extensive and more subtle neuropsychological impairment of internal monitoring, resulting in failure to recognize internally generated mental acts as such, that is, with hyper(dys)-functional left temporolimbic lobes (TLL) and left DLPFC (Liddle et al. 1992).

**Summary of rCBF Studies:**

The Nitric Oxide Hypothesis of rCBF and the Local Circuit Neurons (LCNs)

Hypo(dys)function Hypothesis of Schizophrenia Revisited

Taken together, the rCBF studies reviewed here provide substantial evidence that, compared with normal subjects, schizophrenia patients show a lack of selectively increased neural activity and rCBF in discrete cortical areas such as PFC in response to appropriate activating stimuli. Such a topographically selective and subtle failure, combined with an apparently intact ability to augment blood flow in larger brain volumes, suggests that the microvascular regulatory system rather than the upstream resistance vessels in the above cortical regions might be at fault.

One of the leading hypotheses in the rCBF domain—the nitric oxide hypothesis, briefly reviewed earlier—suggests that the NOS/NADPH-d-positive interneurons may be deficient. In fact, evidence of this deficiency recently became available (Akbarian et al. 1993a, 1993b; Bloom 1993): in postmortem pathology the dorsolateral prefrontal and the lateral temporal lobe regions, including hippocampus cortex and underlying superficial and deep white matter, of schizophrenia patients showed a significant decline in numbers of NADPH-d-positive interneurons in the cortex (especially in superficial layers where they are the last cells to migrate) and in the underlying superficial white matter, and a significant increase of these neurons in the deeper underlying white matter, including the parahippocampal white matter. Akbarian and colleagues (1993a) believe these widespread alterations of cortical ontogenesis, affecting broad regions of the neocortical association fields, are consistent with a neurodevelopmental disturbance of neuronal cell migration and the normal pattern of programmed cell death that is "likely to have serious consequences for the establishment of a normal pattern of cortical connections, leading to a potential breakdown of frontal lobe function in schizophrenia" (p. 169).

There is no evidence that the deficient NOS/NADPH-d nitric oxide-producing interneurons are directly responsible for the rCBF patterns in schizophrenia discussed earlier, but compelling evidence is presented below for the rCBF regulatory role of these neurons (Estrada et al. 1993; Iadecola 1993; Iadecola et al. 1994; Meyer et al. 1994). Initial evidence (Akbarian et al. 1993a, 1993b) is also shown suggesting that incomplete migration has led to the deficiency of...
these interneurons in cerebral areas such as the PFC and TLL (but see also Karson et al. 1994). Recent research on PFC and TLL has resulted in general agreement that deficits in these areas play a major role in the pathogenesis of schizophrenia (Weinberger et al. 1992; Goldman-Rakic 1994; Winn 1994). It remains to be seen if migratory disturbances of the nitric oxide-producing interneurons will be found to be specific for the PFC and TLL areas and whether they will be identified in conditions other than schizophrenia.

Additional evidence recently available from other systems in PFC and TLL areas supports the idea that NOS/NADPH-d neurons are unable to respond to task demands. A large body of data showing glutamatergic deficiency in these areas (for reviews, see Ulas and Cotman 1993; Ishimaru et al. 1994) is consistent with the idea that these neurons may be underresponsive partly because of a glutamate deficiency and may therefore produce even less nitric oxide. Moreover, the second messenger inositol triphosphate (IP3), generated by the phospholipase C second messenger system and controlling, among other things, the release of intracellular Ca++, is a phosphomonoester. Phosphomonoesters are precursors of membrane phospholipids. Magnetic resonance spectroscopy studies (for a review, see Pettergrew et al. 1993) have shown that phosphomonoesters and possibly IP3 (too difficult to measure at present) are decreased in the PFC of schizophrenia patients, whereas phosphodiesters, which are breakdown products of membrane phospholipids, are increased. While this is generally consistent with the hypofrontality hypothesis of schizophrenia, the postulated decrease in Ca++-dependent nitric oxide production in PFC is also consistent with the phosphomonoesters (and, possibly, of IP3) in schizophrenia.

Nitric oxide has been implicated in long-term potentiation as well as in many other central nervous system functions such as neurotransmission, endothelium-derived relaxation, cell-mediated immune response, synaptic plasticity, synaptogenesis, memory formation, neuroendocrine secretion, visual transduction, and olfaction (Schmidt and Walter 1994). The present hypothesis does not limit the proposed deficiency in nitric oxide-producing neurons to those aspects that influence microcirculation but concerns the NOS/NADPH-d interneurons in the prefrontal and temporolimbic lobes of the brain and excludes nitric oxide-producing cells generally.

The single most important factor regulating rCBF is an increase in the volume of blood per minute passing through a certain amount of tissue. This increase usually occurs through dilation of precapillaries and arterioles as well as recruitment and opening of capillaries in each local volume of cerebral tissue undergoing activation (Roland 1993). Objections have been raised about each of the candidates proposed for the regulatory role in cerebral microcirculation (for critical reviews see Iadecola 1993; Roland 1993; Iadecola et al. 1994). For example, rCBF is better correlated with arterial than with tissue pCO2 and can vary independently even of arterial pCO2 in pathological conditions; hydrogen (H+) is unlikely to initiate CBF changes because the increase in rCBF during enhanced brain activity precedes the rise in interstitial H+ concentration; and with O2 the increased brain activity rather than tissue hypoxia increases rCBF and leads to hyperoxia, which remains decoupled from the O2 consumption for some time. A critical summary of the compelling anatomical and physiological evidence supporting nitric oxide as a leading candidate for this role is therefore warranted.

1. The endothelial and neuronal isoforms of NOS are dependent on Ca++ and calmodulin for activation and are constitutively expressed in the cerebral vasculature (in endothelial cells and perivascular nerves innervating large cerebral arteries, including the circle of Willis) and in the neural fibers of cortical and striatal NOS/NADPH-d-positive interneurons whose central processes are closely apposed to intracerebral microvessels (Zhang et al. 1994). The inducible and Ca++-independent NOS isoform is found in macrophages and in many other types of cells able to express cell-mediated immune response. Nitric oxide-synthesizing neurons are therefore in a unique position to exert widespread influence on other cortical neurons as well as on large and local blood vessels, including capillaries.

2. Studies using NOS inhibitors (see Iadecola et al. 1994 for review) as well as electrical stimulation of selected neural pathways have shown that nitric oxide participates in the maintenance of resting cerebrovascular tone and blood flow and in the increase of rCBF under activation (Wang et al. 1994).

3. Excitation of local cortical
neurons by topical application of N-methyl-D-aspartate produces local vasodilation that is reversibly attenuated by NOS inhibitors, suggesting that nitric oxide participates in the response.

4. NOS neurons can produce nitric oxide in response to activation of multiple neural systems, both intrinsic and extrinsic to the cortex; increases in intracellular Ca$$^{++}$$ can also activate NOS and nitric oxide production (Garthwaite 1991) so that synaptic activity taking place on NOS-containing dendritic processes closely apposed to the cerebral microvessels could induce Ca$$^{++}$$ transients in these processes without depolarization of the entire cell.

5. Nitric oxide is highly dippusible in all directions (including the inverse of the vector of the generating signal) and may therefore act as an intercellular messenger by direct diffusion to intracellular targets. It is a potent but extremely short-lived vasodilator (biological half-life, 7 seconds) and is not stored but synthesized on demand.

6. The main objection, however, to nitric oxide as the regulator of rCBF, in addition to the existence of nitric oxide-independent increases of rCBF during neural activity (e.g., during stimulation of the reticular formation), is the fact that rCBF activity has still not been shown to be a linear function of nitric oxide production matching the localization of the NOS.

Moreover, the experience gained from use of NOS inhibitors to ascertain the various roles of nitric oxide is still too new and limited. It is entirely possible that more than one compound (nitric oxide, various transmitters and neuropeptides including catecholamines, glutamate, serotonin [5-HT], substance P [a neuropeptide modulator], etc.) make up the complex system that regulates cerebral microcirculation.

A recent hypothesis concerning the pathogenesis and pathophysiology of schizophrenia discusses the more general role of the nonpyramidal class of frontal lobe cortical neurons and their possible hypo(dys)function in schizophrenia (Bachneff 1991). The LCNs, as these interneurons are often called, make up some of the building blocks of local neuronal circuits and of broadly distributed parallel neuronal networks and may provide a critical component of the neural basis of higher brain functions (Edelman 1978, 1981, 1987, 1993; Goldman-Rakic 1987; Somogyi 1987; Getting 1989; Bullock 1993; Kritzer and Goldman-Rakic 1993). The integrative role of local circuits in transforming complex environmental stimuli into adaptive behavior in simple organisms (Burrows 1992), the regulatory function of local inhibitory circuit neurons in dopamine (DA)- glutamate interactions in rats and monkeys (Kolachana et al. 1993; Krebs et al. 1993), and the pathophysiological importance of PFC and TLL neuronal networks in schizophrenia patients (Liddle et al. 1992; Weinberger et al. 1992, 1993) have recently been recognized.

Recent Developments in LCNs' Characterization. Difficult to study and somewhat neglected in the past despite their numbers, which far surpass the number of sensory and motor neurons put together, the LCNs have gradually been included in the mainstream of neuroscience research, even though their classification is still complicated by the problem of morphological and functional heterogeneity. Patterns of axonal arborization (Jones 1993), scarcity or absence of dendritic spines, patterns of target cell connectivity (Buhl et al. 1994), colocalized Ca-binding proteins and various neuropeptides, and physiological properties have all served as governing principles of classification for these GABAergic nonpyramidal neurons. For an in-depth review, which is outside the scope of this work, see Rakic 1975; Jones 1984, 1988.)

Recent neurophysiological and immunohistochemistry studies (Rogers 1992; Kawaguchi 1993a, 1993b; Kawaguchi and Kubota 1993; Kubota et al. 1993) carried out on the frontal cortex and neostriatum of rats have shown that the architecture of the neocortex and neostriatum is similar with respect to the three identified types of GABAergic interneurons: the fast-spiking, the persistent and low-threshold spike (PLTS), and the calretinin-containing cells. A fourth type of interneurons—the long-lasting afterhyperpolarization cholinergic interneuron—has already been relatively well characterized in the neostriatum (Hendry et al. 1984; Kubota et al. 1993).

The fast-spiking cells (called basket cells by some investigators) exhibit a capacity for consistently more frequent spike firing with virtually no spike frequency adaptation, few or no dendritic spines, and denser axonal arborization near their somata with axons that extend mainly horizontally and parallel to the cortical surface. They are strongly GABAergic, may comprise up to 70 percent of all GABAergic cells (Celio 1986), and contain parvalbumin, which seems to give them the capability for
consistently more frequent discharges. This increased functional capacity has been attributed to the parvalbumin buffering action against increases in intracellular calcium, resulting in a slower outward rate of the potassium currents that precede an eventual firing rate adaptation (Kawaguchi 1993a, 1993b; Kawaguchi and Kubota 1993; Kubota et al. 1993). The preferentially horizontal outlay of fast-spiking cell arbors suggests that only certain cortical layers—those concerned with the treatment of information of similar levels of complexity but that receive information signals through multiple columns—are likely to be inhibited and therefore only the output cells to certain specific targets—those concerned with the execution of certain tasks that tend to be organized in a layer-specific manner—will be suppressed simultaneously.

The PLTS cells show less negative resting potentials than fast-spiking cells, low-threshold discharges at hyperpolarized potentials with burst firing and clear frequency adaptation, a significant number of dendritic spines, and mainly vertically oriented axonal arbors reaching throughout the entire depth of the cortex and into the subjacent white matter. They possess calbindin, show less GABAergic immunoreactivity than fast-spiking cells, and colocalize somatostatin and neuropeptide Y. If the PLTS cells in rat frontal cortex (Kawaguchi 1993a) are similar to those described in rat neo- striatum (Kawaguchi 1993b), they should also be NOS/NADPH-d-positive and therefore capable of releasing nitric oxide. The column-specific vertical outlay of PLTS cell arbors, which enables them to simultaneously influence the column-mediated, increasingly complex levels of information treatment of individual signals in the brain, in conjunction with the presence of at least three neurotransmitters or neuromodulators in addition to nitric oxide, suggests that these cells may have a highly differentiated and subtle impact on neocortical local circuitry and may be a critical part of the local microvascular regulatory system. Cerebral cortex arterioles (20-40 μm in diameter) originate at regular intervals (100-150 μm) from the larger pial arteries and penetrate the substance of the brain down to lamina VI in a fashion parallel to the columns. The PLTS NOS/NADPH-d cell axonal arbors have a similarly fashioned vertical orientation and normally reach throughout the entire depth of the cortex. However, if others confirm Akbarian et al.'s findings (1993a, 1993b) of a significant decline in the numbers of these nitric oxide-producing interneurons in the superficial layers of cortex where they are normally located, it is conceivable that the pattern of frequent microvascular apposition of the NOS-containing processes of the PLTS NOS-containing cells described earlier would be seriously compromised by the partially or totally incomplete migration of these neurons. Such a major alteration in the connectivity of the brain could disrupt cortical arterioles-enhanced nitric oxide diffusion as well as nitric oxide's role as an intercellular messenger regulating the initiation and maintenance of neural activity in PFC and TLL or parts thereof.

The calretinin-positive interneurons have various shapes and strikingly long radial dendrites, and do not show dendritic spines. They occur in all cortical layers but are found mainly in laminae II and III and, in addition to GABA, colocalize vasoactive intestinal polypeptide, especially in the deeper layers (Rogers 1992). It is notable that the Ca-binding proteins parvalbumin, calbindin, and calretinin, and the transmitters and modulators, which occur mainly in the combinations described above with rare cross-colocalization, seem to identify the fast-spiking parvalbumin, PLTS-calbindin, and calretinin cells as distinct subpopulations. However, a recent triple-staining immunohistochemical study of rat pyriform cortex found GABA reactivity to predominate in layer I, whereas parvalbumin and calbindin colocalization with GABA and cross-colocalization in interneurons increased toward layers II and III (Kubota and Jones 1993).

Multiple Interactions of Some Neurotransmitter Systems in the Midbrain, Striatum, and Cortex and Their Relevance to the Pathophysiology of Schizophrenia. Neuronal systems in the brain can be broadly divided into two general categories. Hierarchical systems include the pathways directly involved in sensory perception and motor functions, whose large myelinated fibers are able to process information sequentially, phasically, and quickly. Nonspecific or diffuse neuronal systems have fine and unmyelinated pathways that originate from small nuclei in the brainstem and midbrain, branch in an extraordinarily divergent pattern, and diffuse, but often with certain predilections, innervate almost the entire forebrain (Nicoll et al. 1990). In many instances, clearly identifiable postsynaptic sites are not found in the
vicinity of the neurotransmitter release sites of the diffuse neuronal system fibers, suggesting that the transmitter substances may be diffusely released in the extracellular fluid (Beaudet and Descarries 1978; Garris and Wightman 1994) and that the cellular targets of these nonspecific neuronal systems should be inferred from the location of the receptors and not from the location of the transmitter release sites (Nicoll et al. 1990). Typical representatives of the diffuse neuronal systems are the monoamines DA, serotonin (5-HT), and norepinephrine. Since the signals generated in the central nervous system by these transmitters may affect large brain regions simultaneously, it is important to note not only the predictable involvement they have in global central nervous system functions frequently affected in schizophrenia, such as attention, arousal, sleep, handling of stress, mood, and cognition, but also to review briefly some of the ways in which they interact (for a review of individual transmitter systems, see Nicoll et al. 1990) and why these interactions may be relevant to the pathophysiology of schizophrenia.

**DA-GABA.** It has long been suspected that GABA antagonizes or dampens DA-mediated behaviors (Roberts 1976; Garbutt and van Kammen 1983), but only recently has there been direct evidence for DA-GABA interactions. Available (Finley et al. 1990; Moghaddam et al. 1990; Vincent et al. 1990). According to a recent study, D_1 DA receptors seem to be selectively localized to the midbrain terminals of medium-sized spiny striatal GABAergic neurons that project to the ventral tegmental area and synapse there with GABA_B postsynaptic receptors located on DA neurons. It has been shown that stimulation of these D_1 presynaptic receptors by endogenous DA released from the dendrites of spontaneously active ventral tegmental area DA neurons results in a tonic enhancement of GABA release that modulates the activity of these DA neurons and is in turn modulated by it (Cameron and Williams 1993). Another experiment dealing with GABA_B neurotransmission but using extracellular recording techniques and carried out on rat substantia nigra pars compacta DA neurons, showed that systemic application of baclofen, a GABA_B agonist, produced a reduction in the firing rate of DA neurons and a decrease in burst firing (Engberg et al. 1993). The opposite process (i.e., switching from a single firing mode, which is thought to reflect initiating movements, to a burst mode, possibly related to the attentional and motivational components of behavior), has previously been associated with the activation of glutamatergic corticofugal projections to substantia nigra pars compacta. Taken together, these two studies suggest a GABA_B receptor-mediated mechanism that is able to counterbalance excessive dopaminergic neurotransmission. Paradoxically, administration of muscimol, a GABA_A agonist, increased burst firing of DA cells. This increase could be explained by muscimol’s activation of GABA_A receptors on inhibitory substantia nigra pars reticulata interneurons that would then become hyperpolarized and lead to disinhibition of the neighboring DA neurons in substantia nigra pars compacta. Moreover, DA terminals in the cortex, in addition to synapsing on pyramidal putative glutamatergic cells in deeper cortical layers, primarily with D_1 receptors, were shown to establish direct contacts with D_3 receptors located on GABAergic interneurons in rat’s and monkey’s PFC (Vincent et al. 1992, 1993a, 1993b; Sesack et al. 1993). It follows from the foregoing that even with respect to only the DA-GABA interactions a potentially multifunctional parallel neurocircuit may exist that may conduct or divert to GABA_A or GABA_B receptors’ synaptic inputs originating from discrete afferent neurons (Sugita et al. 1992) and may select, conceivably in various configurations (Getting 1989), distinct subpopulations of LCNs and D_1 or D_2 receptors.

**Acetylcholine DA-GABA.** Acetylcholine was the first compound pharmacologically established as a neurotransmitter in the central nervous system. A correct balance between acetylcholine-DA has long been considered crucial for fine motor control in the striatum. Exogenous acetylcholine has also been known to decrease DA release in the striatum, possibly by mimicking the excitatory output of striatal cholinergic interneurons that would excite the medium-sized spiny GABAergic striatonigral projection neurons and result in inhibition of DA neurons in substantia nigra pars compacta. Muscarinic cholinergic blockade produces an increase in DA release in the striatum and, particularly after high doses of anticholinergics, psychotic symptoms, cognitive deficits of attention and motivation, and a hypofrontal pattern of rCBF (Dewey et al. 1993a). Presynaptic muscarinic M_1 receptors inhibiting GABA release have
been reported on those GABA-containing fibers that participate in GABA_A receptor-mediated neurotransmission circuits in rat lateral amygdala, while presynaptic 5-HT receptors mediate the inhibition of GABA release in rat ventral tegmental area but in GABA_B circuits (Sugita et al. 1991, 1992). These findings prompted the authors to conclude that the GABA_A receptors that are coupled to the fast chloride (Cl^-) channel might be part of the fast hierarchical neuronal systems, while the slower K+ channel-coupled GABA_B receptors might belong to the diffuse regulatory brain systems. Enhancement of GABA release to counterbalance these M_2- and 5-HT-mediated mechanisms could be achieved by the D_1 presynaptic mechanism in ventral tegmental area discussed above.

**Glutamate-DA-GABA.** Studies of the glutamate-DA component of the glutamate-DA-GABA interactions have clearly established that glutamate release from the corticostriatal fibers exerts a direct presynaptic regulation of DA release by stimulating N-methyl-D-aspartate receptors located on nigrostriatal DA terminals (Giorgiueff et al. 1977; Taber and Fibiger 1993). This N-methyl-D-aspartate-evoked release of DA is much more prominent in the sensorimotor cortex-afferented lateralposterior anatomical compartments of the striatum (matrix) than in the PFC- and limbic cortex-afferented medial-anterior compartments (striosomes) (Graybiel 1990), possibly because of a greater density of N-methyl-D-aspartate receptors in the matrix. However, in the presence of bicuculline, a GABA_A antagonist, the stimulating effect of N-methyl-D-aspartate on DA release is inverted, that is, it is much stronger in the striosomes, indicating that the inhibitory local GABAergic control of DA release, possibly provided by a dendritic release of GABA from medium-sized spiny striatal neurons (the main targets of corticostriatal glutamatergic fibers) or by interneurons, is more potent in the PFC- and limbic cortex-afferented striatum (Krebs et al. 1993).

**5-HT-DA-GABA.** The 5-HT pretreatment receptors present on GABA-containing fibers (medium-sized spiny neurons) in the rat midbrain (mentioned above) were shown in another study to inhibit GABA_B (but not GABA_A) neurotransmission to midbrain DA neurons, to increase DA release in the striatum, and to act as 5-HT_1b receptors negatively coupled to adenylyl cyclase (equivalent to 5-HT_1d in man) (Johnson et al. 1992). The ability of 5-HT_1b receptors to inhibit the release of their own transmitter has been well documented in the past. Moreover, it has been shown that the excitatory effect of 5-HT in rat pyriform cortex is mediated by 5-HT_2 receptors. The cells expressing 5-HT_2 receptors have been identified as interneurons, whereas the stimulation of neighboring pyramidal cells by 5-HT has been attributed to 5-HT_1c receptors (Sheldon and Aghajanian 1994). The 5-HT_1b receptors are thought to be the most common 5-HT alteration. Furthermore, it appears that the cortical neurons that most often express 5-HT_2 receptors, at least in rats, are those interneurons (Morilak et al. 1993) that have the highest densities in the limbic system, striatum, and layer IV of the frontal cortex (Nicoll et al. 1990; Morilak et al. 1993) and that the interneurons in rat pyriform cortex that expressed 5-HT_2 showed electrophysiological characteristics (Gellman and Aghajanian 1994) very similar to those described for fast-spiking cells. Moreover, a small population of cells of the pyriform cortex in rats has recently been reported to coexpress 5-HT_2 and DA receptors (Gellman and Aghajanian 1993). In addition, atypical neuroleptic drugs such as risperidone and clozapine, unlike classical neuroleptics, have been reported to fully inhibit 5-HT-induced and 5-HT-mediated firing of cortical interneurons at clinically relevant doses, whereas “DA-mediated excitation of interneurons was exquisitely sensitive to antagonism” by classic antipsychotics such as haloperidol and chlorpromazine (Gellman and Aghajanian 1994, p. 523). This evidence sug-
suggests that the cortical interneurons that coexpress 5-HT₂ and DA receptors may be a likely site for the action of atypical neuroleptics and that the partially overlapping but mainly DA receptor-expressing subpopulations of interneurons (Vincent et al. 1993b) are another likely site for the action of classical antiepiphanergic drugs.

Conclusion

The LCNs hypothesis has received limited or indirect support from recent studies exploring the neurobiological basis of schizophrenia (Benes et al. 1991, 1992; Sherman et al. 1991; Farde et al. 1992; Vincent et al. 1992, 1993a; Breier et al. 1993; Hoffman and McGlashan 1993; Pettenegro et al. 1993; Farde 1993), as well as from our own preliminary PET studies (Reith et al. 1991a, 1991b, 1994). Direct support is provided by the Akbarian et al. (1993a, 1993b) study showing that neurodevelopmental disturbance of an important subset of the LCNs—the PLTS nitric-oxide-producing cells—may have a widespread impact on PFC and TLL neocortical association areas. The hypo(dys)function of the local circuit neurons in PFC and TLL postulated by the LCNs hypothesis could be a result of this migratory neurodevelopmental disturbance. The NOS/NADPH-d, PLTS-, calbindin-, somatostatin-, neuropeptide Y-positive GABA-ergic interneurons in PFC and TLL shown to be deficient in schizophrenia, could be of critical importance for rCBF control in these areas and an essential component of the cerebral microvascular regulatory system. This could explain the subtle inability of schizophrenia patients in the rCBF studies reviewed to selectively activate rCBF in PFC and TLL, whereas the intact capacity of these patients to increase CBF in larger brain volumes could be due to other nondysfunctional factors or regulators of CBF (Iadecola et al. 1993). Nitric oxide deficiency might also affect the other nitric oxide-related functions in PFC and TLL, leading to long-term potentiation deficits in these areas. These deficits might explain the difficulties schizophrenia patients have with tasks related to those PFC and TLL functions that require sufficient neuronal plasticity to allow those modifications of neighboring local neuronal circuits and neuronal networks essential for goal-directed behavior, flexible responding and learning, and other adaptive behaviors. A hypo(dys)function of the fast-spiking, parvalbumin-positive, strongly GABA-ergic cells (e.g., a failure to inhibit a no longer appropriate response in a neurocognitive task such as the WCST) could interfere with the emerging role of GABA₉ receptor-mediated and glutamate, acetylcholine, and 5-HT receptor-mediated neurotransmission in the local neuronal circuits and in the neuronal networks that modulate DA and GABA release and possibly handle the neurochemical concomitants of stress, as shown in the interactions between neurotransmitter systems discussed above. It might also explain the extensively documented difficulties of schizophrenia patients with neuropsychological delayed-response-type tasks that require intact "working" short-term memory (Goldman-Rakic 1987, 1994). Such a selective type of inhibition failure could indicate a layer-specific information treatment failure (Perry and Braff 1994), possibly related to the layer-specific outlay of fast-spiking cell arbors rather than to a PLTS-related column-specific rCBF regulatory failure. The fast-spiking cells' ability to discharge frequently, reliably, and "tirelessly" over time without spike frequency adaptation makes them possible candidates for the role of a cellular substrate in delayed-response tasks where the PFC must retain information "on-line" during a period of delay before a response is made (Winn 1994). A bridge is thus built from perception to action across time, a bridge that epitomizes the nature of these cells and could arguably reflect the neurobiological reason for calling them interneurons. Clearly, however, refinements in the characterization and functional assignment of the various subclasses of LCNs is just beginning. New in vivo research strategies may be able to test the functional integrity (Dewey et al. 1993b) and structural components (Rothman et al. 1993) of the interactive neurotransmitter systems and the local circuits and neuronal networks involved and thus test the LCNs hypothesis more directly.

The LCNs hypothesis, as revised, proposes that hypofunctional or dysfunctional LCNs and local neuronal circuits in the prefrontal and temporo-limbic lobes may be central to the pathogenesis and pathophysiology of schizophrenia. LCNs seem to be a unifying cohesive force that permeates and underlies the four major topics reviewed in this article:

1. The role of nitric oxide in cerebral microvascular regulation. NOS/NADPH-d PLTS nitric oxide-producing cells are LCNs and seem to be deficient in PFC and TLL of schizophrenia patients.
2. PET and SPECT findings in rCBF studies of schizophrenia. A subtle failure to selectively raise rCBF in discrete cerebral regions such as PFC, perhaps resulting from a deficiency of the cerebral microvascular regulatory system related to the nitric oxide-producing cells as well as from a deficit of the glutamatergic cortical neurotransmission, may explain why frontal and prefrontal regions are hypometabolic and hypoperfused.

3. Recent developments in LCNs characterization.

4. Multiple interactions between some neurotransmitter systems in the midbrain, striatum, and cortex. LCNs and local neuronal circuits seem to be an important regulatory interface in such multiple interactions as well as likely sites for the therapeutic action of both typical and atypical antipsychotic drugs. In addition, LCNs may be candidates for the cellular substrate of working memory. Deficiency of the working memory is considered a prominent pathophysiological mechanism in schizophrenia that may explain the often replicated difficulties schizophrenia patients have with delayed response-type cognitive tasks (such as the WCST) as well as other deficiencies in information processing.

Our ongoing experimental approach to testing some of the predictions of the LCNs hypothesis (Bachneff 1991)—which so far has been possible only partially and indirectly—has involved PET brain imaging. Our goals have been to measure the striatal presynaptic DA activity (by estimating the activity of the DA-synthesizing enzyme—dihydroxyphenylalanine (DOPA) decarboxylase—using [18F]-DOPA), the D2 and D1 receptor densities (by estimating Bmax and Kd using [11C]raclopride and [11C]-SCH23390), and the extraneuronal DA concentration following reserpine-induced DA depletion. High-resolution PET or SPECT estimation of 18O- or 99mTc-HMPAO-derived rCBF values, registering them into the standard stereotactic localization for precise neuroanatomical space for precise neuroanatomical localization in the frontal cortex of schizophrenics implies anomalous cortical development. Archives of General Psychiatry, 50:169-177, 1993a.

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