MINIREVIEW

Salsolinol, a Derivate of Dopamine, is a Possible Modulator of Catecholaminergic Transmission: a Review of Recent Developments

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Summary
Catecholamine (dopamine, norepinephrine and epinephrine) synthesizing neurons are widely distributed in the brain, sympathetic ganglia and throughout peripheral organs. Results of several recent experiments clearly suggest that many of these neurons can also contain 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol), a derivate of dopamine. However, direct proof of salsolinol synthesis in those neurons is still missing. The data obtained with administration of exogenous salsolinol strongly indicate that it may play an important role in catecholaminergic regulatory processes, such as the regulation of prolactin release and/or neuronal transmission in sympathetic ganglia. Several recent data have also indicated a relationship between salsolinol or its metabolites and the etiology of Parkinson's disease or neuropathology of chronic alcoholism. These seemingly different roles of salsolinol will be discussed separately, but some common features will also be highlighted. Based on all of the discussed data the existence of a “salsolinolergic” system using salsolinol as a neuromodulator, which may be present in catecholamine synthesizing neurons, is postulated.

Key words
Salsolinol • Dopamine • Prolactoliberin • Parkinson’s disease • 1MeDIQ

Introduction
The neurotransmitters dopamine, norepinephrine and epinephrine are widely distributed in the brain and periphery (Hokfelt et al. 1974, Lindvall and Bjorklund 1978, Bjorklund and Lindvall 1984). Fundamental work on dopamine function by A. Carlsson was awarded the Nobel Prize in 2000 (Carlsson 2001). The brain dopaminergic system is implicated in a variety of physiological and pathophysiological processes. It regulates prolactin secretion, motion, emotion, cognition and functional neuromodulation at many levels of the visual system (Weinberger et al. 1988, Masson et al. 1993, Nieoullon 2002). An imbalance between
dopaminergic neurotransmission and dopamine receptors is known to be associated with the symptomatology of numerous neuropsychiatric disorders, like schizophrenia, psychosis, mania and depression as well as neuropathological disorders, like Parkinson’s disease (PD), neuroathyrm, Huntington’s disease (Carlsson 1988, Bermanohn and Siris 1992, Brown and Gershon 1993, Jakel and Maragos 2000, Kostrzewa and Segura-Aguilar 2003).

Previous studies evaluating the function of salsolinol (1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline), a dopamine-derived endogenously synthesized compound, revealed its involvement in the progression of disease characterized by dysfunction of dopaminergic neurons, as in the case of PD (Moser et al. 1995).

More recent data, however, have indicated that salsolinol might represent a neuromodulator of dopaminergic neurotransmission. These findings suggest that salsolinol may serve as a neuromodulator in the tuberoinfundibular and nigrostriatal dopaminergic systems (Tóth et al. 2001, Naoi et al. 2002). Moreover, there are indications that salsolinol may participate in the regulation of neurotransmission of small intensely fluorescent (SIF) cells in the sympathetic ganglia as well (Bodnár et al. 2004a, Mravec et al. 2004).

This article summarizes the data that suggest the role of salsolinol in catecholaminergic (especially dopaminergic) transmission as well as in the processes that are characterized by a dysfunction of catecholaminergic neurons.

**Biosynthesis of salsolinol**

Salsolinol is an endogenously synthesized catechol isquinoline that has been detected in rat and human brain tissue samples (Sandler et al. 1973, Collins and Bigdeli 1975). Salsolinol can be synthesized from dopamine and acetaldehyde by the enzyme salsolinol synthase. Alternatively, it can also be synthesized from dopamine and pyruvic acid by forming an intermediate metabolite, salsolinol-1-carboxylic acid. Salsolinol-1-carboxylic acid can be directly metabolized by an unknown enzyme to salsolinol or at first to 1,2-dehydrosalsolinol and then to salsolinol (Naoi et al. 1996, 2002) (Fig. 1).

Therefore, it is not surprising that salsolinol and its metabolites can be detected in many areas of the brain that are also rich in dopamine. The highest concentration of salsolinol and its metabolites has been detected in the basal ganglia, especially in the striatum (Mushhoff et al. 1999). It has also been found in the substantia nigra, frontal cortex (Naoi et al. 2002), hypothalamus (Mushhoff et al. 2000), median eminence and in neuro-intermediate lobe of the pituitary gland (Tóth et al. 2001).

Interestingly enough, only (R) enantiomer of salsolinol is present in the brain, however, both (R) and (S) enantiomers are found in human plasma and urine (Naoi et al. 2004). The enantiomer selective occurrence of salsolinol suggests that it is endogenously synthesized in nerve bodies or synaptic terminals of dopamine neurons. Nevertheless, it must be emphasized that the direct evidence is still missing. Moreover, it is known that glial cells are able to take up a wide range of neurotransmitters (Hansson 1985, Inazu et al. 1999, Takeda et al. 2002). Therefore, at present it is not possible to exclude the synthesis and/or uptake of salsolinol by glial cells as well.

**Biodegradation of salsolinol**

Salsolinol is metabolized by the enzyme N-methyltransferase to N-methyl-salsolinol and consequently by amine oxidase to 1,2-dimethyl-6,7-dihydroxyisquinolinium ion (Naoi et al. 2002, 2004) (Fig. 2). It is thought that some metabolites of salsolinol are involved in the etiopathogenesis of Parkinson’s disease (Maruyama and Naoi 2002; for details see below).
Role of salsolinol in catecholamine system dysfunctions

Neurotoxicity of the salsolinol

Neurotoxins, e.g. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPPT), 6-hydroxydopamine (6-OHDA), are chemical substances which have an active role in promoting neuronal necrosis, apoptosis or neurodegenerative processes. Moreover, neurotoxins might also impair nervous system functions by their deleterious effect on neuronal satellite cells (Kostrzewa 1999, Segura-Aguilar and Kostrzewa 2004).

Properties of salsolinol, as a neurotoxin, are intensively studied. Salsolinol has a molecular structure similar to MPPT and also to 6-OHDA, which are known to induce loss of catecholaminergic cells. Salsolinol and/or its methylated derivatives have been suggested to act as endogenous dopaminergic neurotoxins, inducing selective neuronal cell death and eliciting symptoms almost identical to idiopathic Parkinson’s disease (Martinez-Alvarado et al. 2001; for details see next section).

Salsolinol could lead to neurotoxicity in dopaminergic cells by inhibition of mitochondrial complex II (succinate-Q reductase) activity (Storch et al. 2000). In vitro studies have shown that incubation of dopaminergic neuroblastoma SH-SY5Y cells with N-methyl-salsolinol caused cell apoptosis. Moreover, it has been shown that copper accelerates salsolinol-induced PC 12 cells death (Kim et al. 2001).

Salsolinol can trigger typical apoptotic dopaminergic cell death, which appears to be mediated, at least in part, through a reactive oxygen species-activated cascade (Chun et al. 2001). The data indicate that mitochondria are the site which decides the cell death induced by N-methyl-salsolinol (Storch et al. 2000, Naoi et al. 2002). Moreover, it is suggested that salsolinol and its derivatives might induce alteration of protein synthesis in the endoplasmic reticulum (Kheradpezhouh et al. 2003).

The role of salsolinol in Parkinson’s disease

The cause of chronic nigral cell death in PD and the underlying mechanisms remain elusive. The data suggest that exogenous and endogenous neurotoxic substances (e.g. MPTP, 1,1’-dimehtyl-4,4’-bipyridium (paraquat), isoquinoline derivatives) can participate in nigral dopaminergic cell loss (Antkiewicz-Michaluk 2002, Kostrzewa and Segura-Aguilar 2003). Hence, a great part of research dealing with the isoquinoline derivative salsolinol and its metabolites is focused on its involvement in the etiopathogenesis of PD (for review see Dostert et al. 1988, Nagatsu 1997, 2002, Naoi et al. 1997, Antkiewicz-Michaluk 2002).

The data suggest that especially N-methylated derivatives of salsolinol, N-methyl-salsolinol and its metabolite products, might be importantly involved in etiopathogenesis of PD (Maruyama et al. 1997). It has been demonstrated that patients with PD have an increased activity of N-methyltransferase, catalyzing the synthesis of N-methyl-salsolinol from salsolinol, in lymphocytes (Naoi and Maruyama 1999, Maruyama and Naoi 2002, Naoi et al. 2002, 2004). Animal studies showed that the activity of a neutral N-methyltransferase in the striatum was found to determine the level of 1,2-dimethyl-6,7-dihydroxyisooquinolinium ion, an oxidation product of N-methyl-salsolinol in the substantia nigra (Maruyama et al. 2000).

It has also been observed that endogenously synthesized salsolinol and its derivatives (e.g. norsalsolinol, N-methyl-norsalsolinol, N-methyl-salsolinol) are increased in the cerebrospinal fluid (Maruyama et al. 1996) and the urine (Moser et al. 1996) of patients with idiopathic PD. Because norsalsolinol derivatives are found in low or undetectable concentrations in healthy subjects (Niwa et al. 1991) the role as a biological marker for PD has been proposed (Moser et al. 1995). However, recent data indicate that the observed...
increase of systemic levels of norsalsolinol derivatives are induced by levodopa treatment and do not represent an accurate biological marker of PD (Scholz et al. 2004).

It can be supposed that salsolinol is synthesized in terminals of dopaminergic cells of the substantia nigra, where its presence has already been proven (Naoi et al. 2002). Thus, it can participate in the regulation of the nigrostriatal system activity. During unfavorable conditions, salsolinol and/or one of its metabolites can participate in the etiopathogenesis of PD (Maruyama et al. 1997). Therefore, as far as the search and development of new drugs for the treatment of PD is now focusing on compounds exhibiting neuroprotective and anti-apoptotic influence against N-methyl-salsolinol (Naoi et al. 2000, Maruyama et al. 2004, Yi et al. 2005).

In addition to the loss of dopaminergic cells in substantia nigra (Bernheimer et al. 1973, Damier et al. 1999), reduction of the number of catecholaminergic neurons in the locus coeruleus, subcoeruleus, retrorubral nucleus and ventral tegmental areas was found (German et al. 1989, 1992). Whether salsolinol, or its metabolites, are responsible for the loss of catecholaminergic neurons in these brain areas remains to be answered.

**The role of salsolinol in autonomic dysfunction in PD**

Variable dysfunctions of autonomic system have been recognized in patients with PD, including cardiovascular symptoms, gastrointestinal, urogenital, sudomotor and thermoregulatory dysfunction, papillary abnormalities as well as sleep and respiratory disorders (Micieli et al. 2003).

It is believed that orthostatic hypotension, common in PD patients, is a consequence of chronic L-DOPA treatment. Recent studies showed that orthostatic hypotension is most likely the result of cardiac sympathetic denervation in PD (Li et al. 2002, Goldstein 2003). Patients with PD having sympathetic neurocirculatory failure also show a significant decrease in 6-[18F]fluorodopamine-derived radioactivity in the heart that is a marker for the reuptake activity of sympathetic nerve endings. These data clearly indicate a reduction of sympathetic terminals in the heart of patients with PD (Goldstein et al. 2000).

The heart is not the only destination of axons of catecholaminergic neurons. It also contains cells, synthesizing catecholamines called small intensely fluorescent (SIF) cells (Slavíková et al. 2003). A population of dopaminergic SIF cells can be detected in the heart atria (Baptista and Kirby 1997).

A possible involvement of salsolinol in the physiological regulation of heart function has already be evaluated in *in vitro* experiments. Salsolinol produces a dose-dependent positive inotropic effect on isolated guinea pig myocardium and a positive chronotropic effect on isolated and perfused rat heart. These data suggest that salsolinol might influence heart rate and contractility acting as β-receptor agonist, especially because this effect could be antagonized by propranolol (10 μg/ml). At the same time the chronotropic effect of salsolinol is potentiated by naloxone, an opioid receptor antagonist (Chavez-Lara et al. 1989, Sokolova et al. 1990). Therefore, it can also be hypothesized that the decreased 6-[18F]fluorodopamine-derived radioactivity in the heart of patients with PD is due to the reduction of dopaminergic SIF cell population, and that salsolinol or one of its derivates may participate in this process by a similar effect to that of different neurotoxins that results in a loss of dopaminergic cells of substantia nigra.

Interestingly enough, it has been observed that salsolinol and some of its metabolites may increase or decrease the formation of hydroxyl radicals, so that they might be neuroprotective or neurotoxic, respectively, and thus might represent a “double faced” molecule. It has been already hypothesized that a disproportion in the ratio of the neuroprotective to the neurotoxic effect of salsolinol might participate in the pathogenesis of PD (Maruyama et al. 1995).

**The role of salsolinol in addiction**

Dopaminergic neurons of the ventral tegmental area (constituting mesocorticolimbic systems) together with endogenous opiates and gama-aminobutyric acid play an important role in the resulting addiction (Koob 1992, Schultz et al. 1997, Kelley and Berridge 2002). It has been suggested that salsolinol, a condensation product of the alcohol metabolite acetaldehyde and dopamine (Fig. 1), may be involved in the balance of the reward systems. The intracranial self-administration technique has shown that salsolinol induced reinforcement in the nucleus accumbens shell of rats at concentrations that are pharmacologically possible. These reinforcing actions are mediated in part by D2/D3-like receptors (Rodd et al. 2003).

*In vitro* data showed a significant decrease of pro-opiomelanocortin gene expression caused by salsolinol. This suggests a possible involvement of salsolinol in the establishment of opioid deficiency in
alcoholism (Putscher et al. 1995). These findings indicate that the rewarding effect of salsolinol may involve mu-opioid receptors (Matsuzawa et al. 2000). Salsolinol can also induce a reduction of receptor affinity for its ligand in the opioid system by a down regulation process due to the continuous opiate receptor stimulation, occurring after ethanol administration (Lucchi et al. 1982). The data suggest that salsolinol may also have a modulatory role on benzodiazepine receptors in the brain (Kuriyama et al. 1987).

Elevated concentrations of salsolinol have been determined in the blood plasma of alcoholics. However, due to a high inter-individual variance in urine salsolinol concentration, it is not a sufficient marker for distinguishing between alcoholics and non-alcoholics (Musshoff 2002). Similarly, a recent finding has shown the lack of a significant association between alcohol consumption and salsolinol formation (Musshoff et al. 2005).

The role of salsolinol in physiological regulatory processes

Release of prolactin

Prolactin (PRL) secretion is under a dominant and tonic inhibitory control of dopamine released from terminals of the hypothalamic neuroendocrine dopaminergic (NEDA) system (Freeman 2000).

Several studies performed by Nagy and his associates during the last few years have clearly indicated that salsolinol may represent at least one of a long suspected neuro-intermediate lobe (NIL) derived prolactoliberin, detected in the perchloric acid extracts of the NIL (Tóth et al. 2001). They have also shown that salsolinol is present in the median eminence and also in the anterior lobe of the pituitary gland. It is well known that these regions are the terminal fields of the NEDA system (Tóth et al. 2001). Furthermore, the salsolinol concentration is elevated during situations when PRL secretion is increased from the anterior lobe of the pituitary gland (Tóth et al. 2001). Moreover, administration of salsolinol to rats and/or mice significantly increases plasma levels of PRL without having any effect on other known pituitary hormones (Tóth et al. 2001).

Molecular structure of the receptor that might mediate the prolactoliberin effect of salsolinol is not yet fully known. However, it has been shown that salsolinol is unable to displace D1 and D2 antagonists (3H-SCH23390, 3H-spiperone). At the same time, it is able to displace some agonists of the α2-adrenoceptors, such as 3H-clonidine as well as 3H-apomorphine, a ligand of the D2 dopamine receptor family in the nanomolar range (Antkiewicz-Michaluk et al. 2000, Tóth et al. 2002, Vetulani et al. 2003). These data suggest that the salsolinol-induced increase of PRL secretion is mediated through its binding to a specific binding sites, which can also recognize dopamine as a signaling molecule, although, its property differs from any of the known dopaminergic receptors (Tóth et al. 2002, Homicsko et al. 2003). More recently it has been shown that a cAMP-coupled mechanism is probably involved in the prolactin releasing action of salsolinol (Radnai et al. 2005), suggesting a receptor-mediated change in cAMP.

The regulation of PRL secretion is rather interesting. On one hand, dopamine acts as a “prolactostatin”, on the other hand its metabolite, salsolinol, acts as a “prolactoliberin”. Consequently it can be supposed that the ratio of dopamine to salsolinol synthesis and release from the NEDA system represents a sophisticated and physiologically economic mechanism for the regulation of PRL release.

Inhibition of sympathoadrenal system activity during stress

Intraperitoneal application of salsolinol effectively reduces both plasma epinephrine (EPI) and norepinephrine (NE) levels during stressful situations in rats (Bodnár et al. 2004a). The immobilization procedure represents one of the strongest stressors, eliciting a huge increase in plasma levels of both EPI and NE (Kvethanský et al. 1978). However, salsolinol administration before or during immobilization almost completely prevents the immobilization-induced increase in plasma catecholamines (Bodnár et al. 2004a). The results obtained from these experiments suggest that salsolinol may be able to act at the level of sympathetic ganglia (Mravec et al. 2004). It can probably influence the dopaminergic SIF cells regulating synaptic transmission between preganglionic and postganglionic neurons (Matthews 1989, Heym et al. 1993, 1994, Tanaka and Chiba 1991, 1996).

Therefore, it can be hypothesized that salsolinol participates in the physiological regulation of the sympathoadrenal system activity and prevents over-activation of this system during episodes of acute stress.

Salsolinol might potentially influence sympathoadrenal system activity also via modification of
catecholaminergic transmission in areas of central nervous system. Hypothalamic paraventricular nucleus (PVN) represents a brain area that participates importantly in the regulation of sympathoadrenal system activity (Kenney et al. 2003). Exposure of animals to stress is accompanied by an increased release of catecholamines in PVN (Pacák et al. 1995, Pacák 2000). Whether endogenously synthesized salsolinol might influence NE-mediated processes in PVN and consequently in the activity of the sympathoadrenal system needs further investigation.

1-methyl-3,4-dihydroisoquinoline (1MeDIQ) – a useful tool for study of salsolinol functions in the organism

1MeDIQ (Fig. 3) is a structural analogue of salsolinol that dose-dependently antagonizes salsolinol-induced PRL release. The administration of 1MeDIQ blocks stress and suckling-induced PRL release (Bodnár et al. 2004b). Moreover, it has an opposite effect on catecholamine secretion than salsolinol. Administration of 1MeDIQ increases both EPI and NE secretion from the adrenal medulla and sympathetic terminals of otherwise non-stressed animals (Mravec et al. 2004).

The administration of 1MeDIQ elicits an increase in motor activity of rats and mice (Fekete et al. unpublished observations). It can be hypothesized that the observed increase in motor activity may be a result of the antagonisms of 1MeDIQ on salsolinol-mediated regulation of the motor system in basal ganglia (Vetulani et al. 2001).

Based on the above described data, it seems that 1MeDIQ is a potent antagonist of most of the known salsolinol-induced biological responses. Therefore, 1MeDIQ might offer an important tool for studying the site and mechanism of action of salsolinol.

Conclusions

It has been shown that salsolinol, a derivative of dopamine, is related to nervous structures of catecholamine neurons and their terminal fields (Musshoff et al. 1999, 2000, Tóth et al. 2001, Naoi et al. 2002) (Fig. 4). Convincing experimental data suggest that salsolinol may be involved in the dopaminergic regulatory processes of both prolactin secretion and sympathoadrenal system activity (Bodnár et al. 2004a, 2004b).

There are indications that salsolinol may play a role in the regulation of other processes and may also be influenced by the dopaminergic system (Antkiewicz-Michaluk et al. 2000, Vetulani et al. 2003). Salsolinol, therefore, can potentially represent a neuromodulator, which participates in the equilibrium of transmission of information at synapses composed of presynaptic neurons synthesizing dopamine as their primary neurotransmitter. In addition, salsolinol can affect levels of monoamine neurotransmitters by inhibiting enzymes related to the metabolism of catecholamines and indoleamines (Naoi et al. 2004). Whether salsolinol might be synthesized in other than dopaminergic neurons (e.g. noradrenergic or adrenalinergic) remains to be answered.

Remarkably, there are some similarities between the neuromodulator role of salsolinol and L-DOPA (Misu et al. 1995, 1996, Tedroff 1997). Both affect receptor status, enzyme activity of the catecholamine biosynthesis as well as mitochondrial metabolism. Similar to the above discussed effects of salsolinol, administration of...
exogenous L-DOPA affects dopamine receptor status, aromatic amino acid decarboxylase (AADC) activity and mitochondrial oxidation in experimental animals (Opacka-Juffry and Brooks 1995). Nevertheless, further similarity that receptor and/or transporter for either L-DOPA or salsolinol have not yet been unequivocally determined (Misu et al. 1996, Ishiiia et al. 2000, Sugaya et al. 2001).

It is also supposed that salsolinol may be involved in processes characterized by an altered function of dopaminergic cells, as in the case of Parkinson’s disease or alcoholism (Dostert et al. 1988, Putsher et al. 1995, Naoi et al. 1997, Antkiewicz-Michaluk 2002). There is also an important question whether salsolinol can participate in the pathogenesis of other diseases characterized by dysfunctions of dopaminergic neurotransmitter systems in the brain or at certain peripheral locations, as in schizophrenia or Huntington’s disease. Based upon the findings that salsolinol may represent a “double-faced” molecule having neuroprotective as well as neurotoxic properties, the manifestation of its “good or bad” influence may depend on hitherto non-specified factor (Maruyama et al. 1995).

At the same time, there is no doubt that salsolinol meets some of the criteria that are necessary for fulfilling the definition of a neurotransmitter/neuromodulator function (Schwartz 2000, Deutch and Roth 2003). It is synthesized in neurons, exogenous application elicits a specific effect and is present a biodegradation pathway for termination of its effect and elimination (Toth et al. 2001, Naoi et al. 2002). In addition, the effect of salsolinol on prolactin secretion as well as on sympathoadrenal system activity can be blocked by an antagonist of the transmitter (1MeDIQ) in a dose-dependent manner (Bodnár et al. 2004a, Mravec et al. 2004). It must be emphasized that many questions still remain to be answered for salsolinol to be considered as a neurotransmitter or neuromodulator. For example, at present it is difficult to localize the distribution of salsolinol and its relationship with the known catecholaminergic transmitters (dopamine, norepinephrine). The gene sequence of the enzyme responsible for salsolinol synthesis is still unknown. However, it is possible to study the alteration of salsolinol-regulated functions after application of its antagonist (1MeDIQ), which can help to highlight the possible site of salsolinol action.

The consideration of salsolinol as a neuromodulator of catecholaminergic neurotransmission might stimulate further research. It could have a positive influence on the development of a new generation of drugs affecting salsolinol-modulated catecholaminergic functions.

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