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REVIEW ARTICLE

Not Just from Ethanol. Tetrahydroisoquinolinic (TIQ) Derivatives: from Neurotoxicity to Neuroprotection

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Abstract

The 1,2,3,4-tetrahydroisoquinolines (TIQs) are compounds frequently described as alkaloids that can be found in the human body fluids and/or tissues including the brain. In most circumstances, TIQs may be originated as a consequence of reactions, known as Pictet-Spengler condensations, between biogenic amines and electrophilic carbonyl compounds, including ethanol's main metabolite, acetaldehyde. Several TIQs may also be synthesized enzymatically whilst others may be formed in the body as by-products of other compounds including TIQs themselves. The biological actions of TIQs appear critically dependent on their metabolism, and nowadays, among TIQs, 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol), N-methyl-1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (N-methyl-(R)-salsolinol), 1-[(3,4-dihydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol (norlaudanosoline or tetrahydropapaveroline or THP) and 1-benzyl-1,2,3,4-tetrahydroisoquinoline (1BnTIQ) are considered as those endowed with the most potent neurotoxic actions. However, it remains to be established whether a continuous exposure to TIQs or to their metabolites might carry toxicological consequences in the short- or long-term period. Remarkably, recent findings suggest that some TIQs such as (1-[(4-hydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol) (higenamine) and 1-methyl-1,2,3,4-tetrahydroisoquinoline (1-MeTIQ) as well as N-methyl-tetrahydroisoquinoline (N-methyl-TIQ) exert unique neuroprotective and neurorestorative actions. The present review article provides an overview on these aspects of TIQs and summarizes those that presently appear the most significant highlights on this puzzling topic.

Keywords Tetrahydroisoquinolines · Ethanol · Neurotoxicity · Neuroprotection

Introduction

The 1,2,3,4-tetrahydroisoquinolines (TIQs, Fig. 1) are compounds described frequently as alkaloids that can be found in the human body as well as in fluids and/or tissues (Dostert et al. 1988) including the brain (McNaught et al. 1998). In most circumstances, TIQs may be originated as a consequence of condensation reactions between biogenic amines (such as phenylethylamines and catechol amines) and a number of other electrophilic, reactive compounds such as aldehydes, α-keto acids (including ethanol metabolites), organic solvents and anesthetic gases (Smargiassi et al. 1994) (Fig. 2) by the known Pictet-Spengler (condensation) reaction (Haber et al. 1997; McNaught et al. 1998). However, some studies have suggested that several TIQs may be also synthesized enzymatically (Fig. 2) (Yamakawa and Ohta 1997, 1999; Naoi et al. 2004) whilst others may be formed in the body as by-products of other compounds (Katagiri et al. 2010).

The physiological role(s) of TIQs has long been an issue of controversy, as discussed by Grobe et al. (2010) and by Stefano et al. (2012). The present work aims at broadcasting an exhaustive critical analysis of the literature on this subject from the point of view that TIQs, depending on their substituents, chemical structure and origin, may have adverse, toxicological properties (Fig. 3) but also, as recently pointed out

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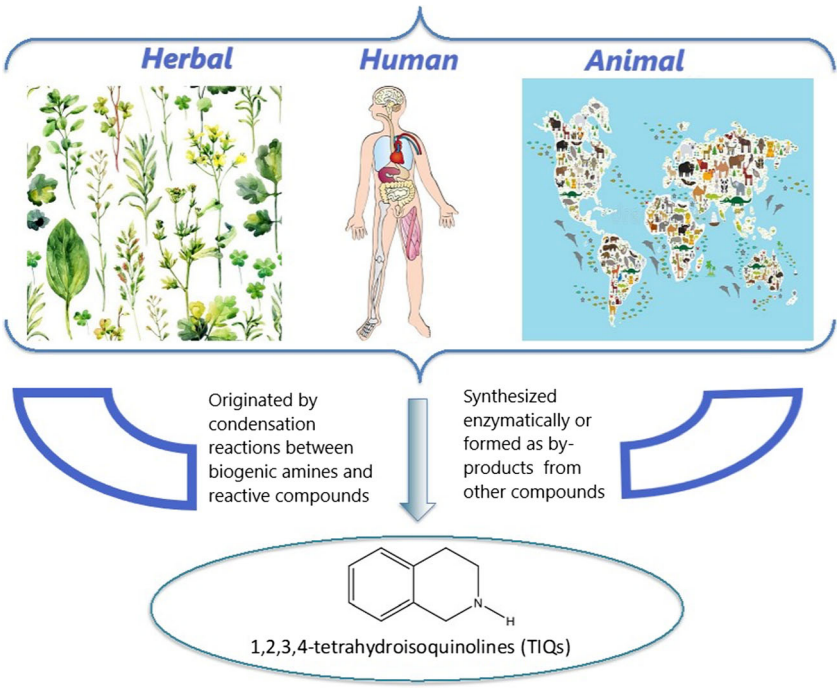

Fig. 1 Pathways of TIQs production

for higenamine, 1-MeTIQ and N-methyl-TIQ, positive, potentially therapeutic applications (Fig. 4). In this regard, the present review represents the first attempt, to the best of our knowledge, to frame these interesting molecules into a comprehensive standpoint.

Tetrahydroisoquinolines

A traditional nomenclature distinguishes TIQs as compounds with catechol and non-catechol structure (Antkiewicz-Michaluk et al. 2014). Several TIQs cross the blood-brain barrier (Makino et al. 1988; Song et al. 2006) and have been suggested to act as false neurotransmitters (Haber et al. 1997), being reportedly taken up, stored and released from presynaptic neurons and hence being potentially able to interfere with central, in particular catecholaminergic, neurotransmission (Greenberg and Cohen 1973). Moreover, early studies on some TIQs suggested an opioid involvement in their actions (Blum 1988) as well as a neuroleptic-like profile attributable to their properties as dopamine (DA) receptors antagonists in rodents (Ginos and Doroski 1979) and a profile as potential N-

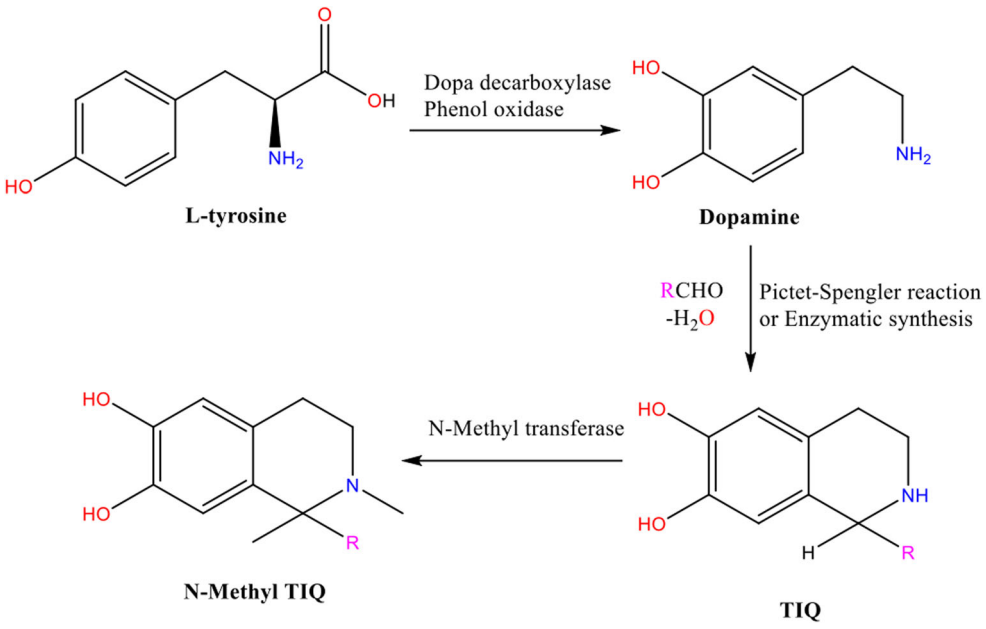

Fig. 2 TIQs origins as a consequence of condensation reactions between biogenic amines (i.e. dopamine) and electrophilic compounds (i.e. acetaldehyde) by the Pictet-Spengler reaction or by enzymatic synthesis

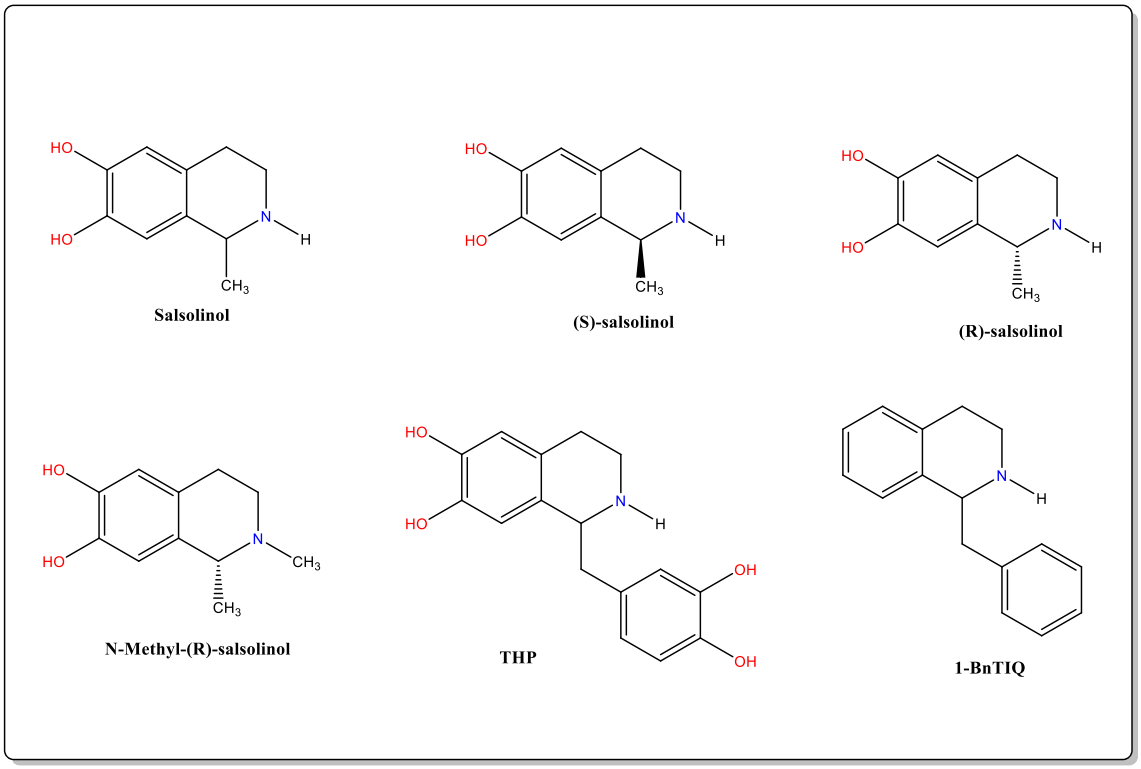

Fig. 3 Neurotoxic TIQs: 1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (Salsolinol), (S)-Salsolinol and (R)-Salsolinol, N-Methyl-1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (N-methyl-(R)-salsolinol), 1-[(3,4-dihydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol (Norlaudanosoline or Tetrahydropapaveroline or THP) and 1-benzyl-1,2,3,4-tetrahydroisoquinoline (1-BnTIQ)

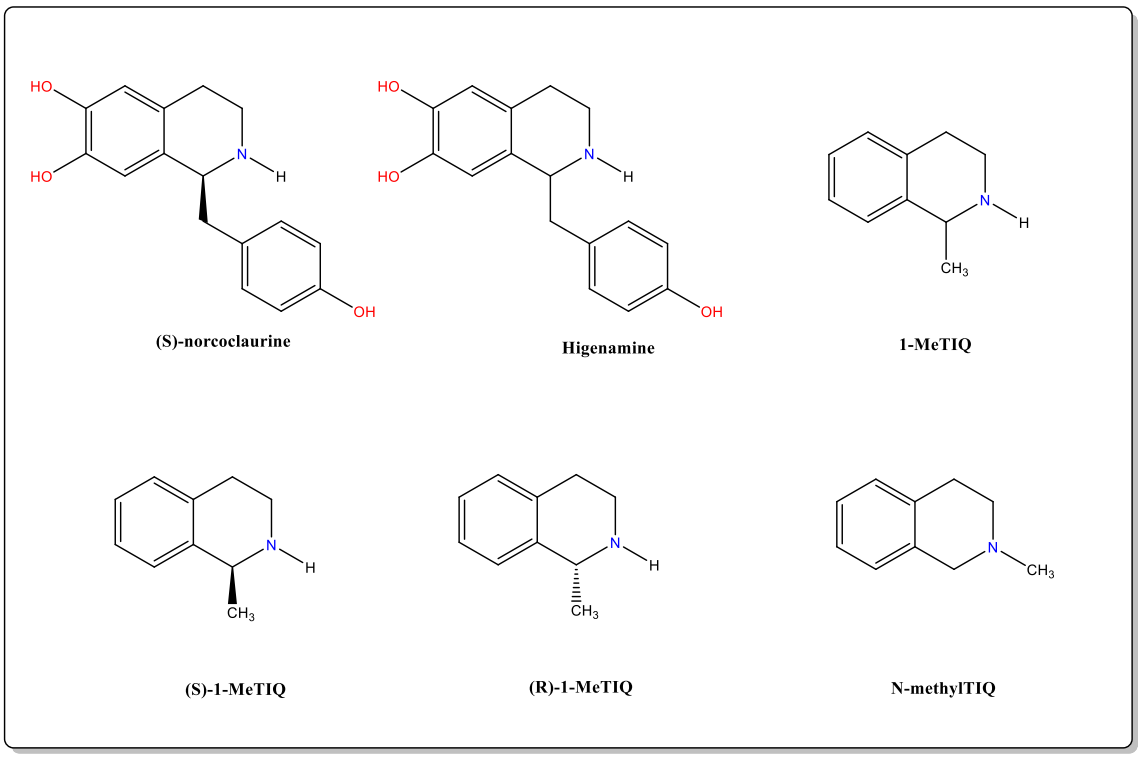

Fig. 4 Neuroprotective TIQs: 1-(4-hydroxyphenyl)methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol ((S)-norcoclaurine), (1-[(4-hydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol) (Higenamine) and 1-methyl-1,2,3,4-tetrahydroisoquinoline (1-MeTIQ), (S)-1-MeTIQ, (R)-1-MeTIQ, as well as N-methyl-tetrahydroisoquinoline (N-methyl-TIQ)

methyl-D-aspartate (NMDA) receptor antagonists (Ortwine et al. 1992) and as antagonists of the phencyclidine (PCP) site (ffrench-Mullen and Rogawski 1989).

Most of the TIQs found in the brain are nowadays commonly recognized as endogenous neurotoxins with neurochemical properties similar to those of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the also structurally similar compound most famous for causing Parkinson's disease (PD) (Herraiz 2016). Interestingly, as it occurs with MPTP, important differences may be related to the enzymes involved in the mechanisms of toxicity (Herraiz 2016); in particular, TIQs can be metabolically activated by conversion into potentially toxic substances, although one of the most striking differences with respect to MPTP refers to the fact that TIQs-induced neurotoxicity is relatively weaker compared to that induced by MPTP (Chiba et al. 2015). Notably, MPTP and its oxidation by-product, 1-methyl-4-phenylpyridinium cation (MPP^+), are selective DArgic neurotoxins that when administered directly into the mice brain induce neuronal degeneration that can provide the experimental animal models of parkinsonism extensively used to investigate the mechanisms underlying neurotoxicity and neurodegeneration as well as to find drugs able to exert neuroprotective effects against oxidative stress-mediated neurotoxicity (Chiueh et al. 1984; Jackson-Lewis and Przedborski 2007).

Characterized by a gradual and selective loss of DArgic neurons, although the origin of this loss remains to be fully established, parkinsonism can also be considered as a neurodegenerative process induced by endogenous neurotoxic substances (Maruyama et al. 2000; Jellinger 2017). In this regard, biologically effective TIQs raise a wide interest, since in in vivo studies they have been found responsible of functional symptoms, such as muscular rigidity, and biochemical changes, including reduced DA levels in the brain, characteristic of PD (Antkiewicz-Michaluk 2002). In particular, among the TIQs of greatest interest, salsolinol and 1-BnTIQ (Fig. 3) have been reported as those with the most prominent neurotoxic action (Antkiewicz-Michaluk 2002). Moreover, as it will be underlined in the following of this review, the consequences of TIQs metabolic fate appear critical for the biological and toxic actions of these compounds. As an example, although CYP enzymes usually metabolize these substances into by-products that lack of toxicity (Herraiz 2016), other biotransformation (enzymatic bio-activation such as those mediated by monoamino oxidases (MAO), N-methyltransferases and peroxidases) turns these compounds into toxins. Moreover, it remains to be established whether a continuous exposure to TIQs, as it may also take place through the intake of foods, might provide their toxic cationic by-products in a concentration critical to carry toxicological consequences in the short- or long-term period. Nevertheless, in spite of these suggestions, the in vivo significance of the conversion of TIQs into cationic, electrophilic and highly reactive species is still fully to be determined and further investigations are necessary to confirm the presence and biological/toxicological significance of these cationic derivatives in the human brain (Herraiz 2016). In addition, TIQs and other DA-derived alkaloids have been described as weak MAO inhibitors due to their ability to influence DA catabolism and reversibly inhibit the MAO-dependent oxidative pathways (Dostert et al. 1988; Antkiewicz-Michaluk et al. 2001). Likewise, it has also been reported that some natural TIQ-like alkaloids show antitumor, anti-microbial, anti-inflammatory, analgesic and anti-HIV-1 activities (Kashiwada et al. 2005; Diamond and Desgagné-Penix 2016). Remarkably, recent findings suggest, instead, that some TIQs, in particular 1-MeTIQ (Fig. 4), may exert exceptional neuroprotective and neurorestorative actions, raising fresh interest on these molecules and opening an exciting new line of future investigations (Antkiewicz-Michaluk et al. 2014; Herraiz 2016; Wąsik et al. 2018a, b).

Ethanol and TIQs

It is well known that ethanol induces neuronal damage and that several processes might be responsible for this ethanol-related adverse effect (Shea et al. 2012) although the mechanism(s) are not completely understood. The deleterious effects of ethanol could be mainly attributed to acetaldehyde (Vaglini et al. 2013), the ethanol's first metabolite that can interact, under certain conditions, with endogenous biogenic amines to generate TIQs (Fig. 2) (Amit et al. 1977; Correa et al. 2012; Hipólito et al. 2012; Berger et al. 1982). On the other hand, Mao et al. (2013) suggested that ethanol-induced alteration of monoamine metabolism and the increase, in particular, of DA-derived catechol (including salsolinol and N-methyl-salsolinol, Fig. 3) could play a role in the development of dysfunctions of monoaminergic neuronal systems (Mao et al. 2013). Some endogenous alkaloids, like salsolinol and 1-[(3,4-dihydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol (THP, Fig. 3), whose blood levels are increased upon ethanol intake, have neurotoxic effects (Surh and Kim 2010). Interestingly, as observed by Collins et al. (1990), the elevations of endogenous TIQs' concentrations, due to prolonged ethanol intake, could depend on a number of factors including the brain region analysed, the duration of intake, and even on the associated dietary constituents. As reported by Collins's group (Collins et al. 1990), the higher striatal GC/MS measurements of salsolinol and related isoquinolines in adult rats drinking ethanol ad libitum could have been facilitated by 3,4-dihydroxyphenylalanine (DOPA) and perhaps by salsolinol itself consumed through the intake of lab chow (Fig. 5). On the other hand, the research on TIQs showed that salsolinol and THP, dose-dependently, increase ethanol intake in response to their infusion in rats (Amit et al. 1977), and coherently with these premises, it was also

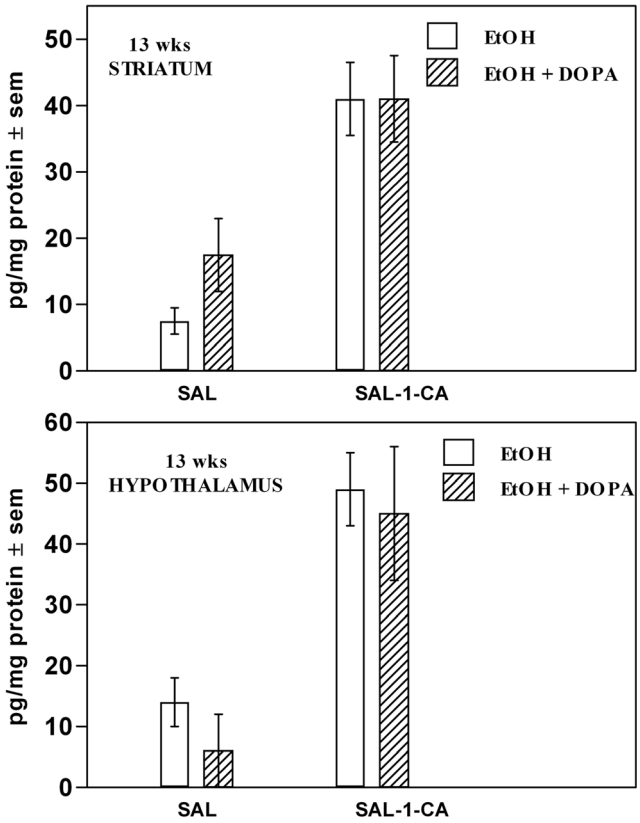

Fig. 5 Effect of daily supplementation with L-DOPA (500 μg/rat) on the concentrations of salsolinol and salsolinol-1-carboxylic acid expressed as picogram/milligram of proteins, in the striatum and hypothalamus of rats consuming ethanol (EtOH)-containing liquid diet for 13 weeks. $N = 6$ pooled samples/group. $*0.07 > p > 0.05$ (one-tailed Student's t test). Reproduced with permission from Collins et al. (1990)

suggested that these TIQs might contribute to induce addiction and, consequently, withdrawal symptoms (Amit et al. 1977), a hypothesis that has never been confirmed so far (see Correa et al. 2012 for an extensive discussion). More recently, Vaglini et al. (2013) reported that ethanol-derived acetaldehyde is able to enhance the toxin-related parkinsonism. Several in vivo and in vitro studies led to the assumption that CYP2E1 may increase MPTP-mediated toxicity in mice by increasing free radical production in DArgic neurons (Vaglini et al. 2013). As a matter of fact, ethanol is a good substrate for the CYP2E1 isoform of CYP_{450} and by this way it may facilitate the susceptibility of DArgic neurons to toxic events (Vaglini et al. 2013). Accordingly, a recent study reported a decreased methylation of the CYP2E1 gene (indicative of an activation of gene transcription) and an increased expression of CYP2E1 mRNA in the brain of PD patients (Kaut et al. 2012). Vaglini et al. (2013) also suggest that epigenetic variants of this cytochrome might contribute to the increased susceptibility to the neurotoxic consequences of ethanol exposure, therefore confirming multiple lines of evidence, in support of the existence of a link between environmental toxins and PD. Moreover, also the aldehyde dehydrogenase inhibitor, disulfiram, was suggested to be responsible of an increase of acetaldehyde that, in turn, may result in a toxic outcome in the clinic (parkinsonism) (Zuddas et al. 1992).

All this notwithstanding, available evidence indicates that a small consumption of ethanol could have a variety of beneficial effects on health including cardiovascular and/or neuroprotective ones (Collins et al. 2009; Poli et al. 2013; Pavey et al. 2018).

Salsolinol

Salsolinol (Fig. 3) possesses an asymmetric centre at C-1 and as a consequence it exists as R and S enantiomer as shown in Fig. 3. As racemic mixture of enantiomers, salsolinol can be formed non-enzymatically by the Pictet-Spengler reaction of DA with acetaldehyde (Fig. 2) (Cohen and Collins 1970) or from pyruvic acid followed by decarboxylation (Dostert et al. 1988; Chen et al. 2018). Whilst, the stereo-selective enzymatic synthesis from DA via (R)-salsolinol synthase is supposed to generate the (R)-enantiomer (Fig. 3) (Chen et al. 2018; Naoi et al. 1996).

Interestingly, (R)- and (S)-salsolinol (Fig. 3) levels, formed in many plant- and protein-derived food sources, such as mushrooms, cocoa powder, cheese, flour, bananas, eggs, fish, milk or beer, cannot be ignored (Kurnik-Łucka et al. 2018), the R- enantiomer of salsolinol being more potent and present in greater concentrations than the S- form. For many years, mostly due to limitations of the available analytical methods, it was thought that (R)-salsolinol should be the only enantiomer present in human brain tissue. In this respect, it has been reported that the R-enantiomer predominates in urines of healthy volunteers, whereas the S-enantiomer predominates in port wine and possibly in other beverages and foods, suggesting that salsolinol present in human bodies could have, at least partially, an endogenous enzymatic origin (Chen et al. 2018), as previously suggested by Collins et al. (1990). These experiments have shown that co-administration of small doses of L-DOPA with the ethanol/liquid diet led to an increased striatal concentration of salsolinol as shown in Fig. 5 (Collins et al. 1990). On the other hand, it is also uncertain whether exogenous salsolinol (delivered from food) can cross the blood-brain barrier (Kurnik-Łucka et al. 2018). Strikingly, the supplementation with DOPA in ethanol-liquid diet brought about a significant increase of the extent of neurodegeneration (Collins et al. 1990). These findings were interpreted as indicative of the fact that in chow-fed and chronically ethanol-treated rats, DA made available in the blood-brain barrier, by decarboxylation of the administered or ingested DOPA, could condensate with acetaldehyde in the cerebrovascular district, or perhaps by a lower extent within the brain, to yield salsolinol (Collins et al. 1990). Likewise, consistently with

Collins et al. (1990), Lee et al. (2010) reported that salsolinol from dietary sources is the major contributor to plasma salsolinol concentrations, specifying that the maximal levels of endogenous salsolinol in mouse striatum homogenates could be obtained after an intraperitoneal administration of ethanol and L-DOPA in the presence of MAO (pargyline) or COMT (tolcapone) inhibitors (Lee et al. 2010).

Salsolinol was also thought responsible of contributing to degeneration of DArgic neurons in the onset and progression of parkinsonism (Chen et al. 2018). On the other hand, Krygowska-Wajs and collaborators (Krygowska-Wajs et al. 1997) reported that the levels of endogenous salsolinol were correlated to the degree of PD and cannot be affected by L-DOPA treatment in patients with different degrees of parkinsonism (Krygowska-Wajs et al. 1997). This would be to say that acetaldehyde itself does not have a role, in spite of its high reactivity and, in this regard, it is still unknown under which conditions DA might lead to salsolinol synthesis and whether, to exert its neurotoxic effects, acetaldehyde originates from ethanol-independent cellular metabolism (as discussed in Peana et al. 2017) or from the central and/or peripheral metabolism of ethanol. Accordingly, numerous hypotheses regarding its pathophysiological role(s) have been raised, especially related to PD and alcohol addiction (Hipólito et al. 2012; Vaglini et al. 2013). All this notwithstanding, on the basis of above-mentioned structural, and possibly mechanistic, similarities between salsolinol and MPTP, it has been reported that repeated administration of salsolinol to mice and rhesus monkeys is responsible of inducing a PD-like behaviour linked to DA oxidation and to the generation of reactive oxygen species (ROS) (Wąsik and Antkiewicz-Michulak 2012). These, in turn, support the formation of by-products that may result detrimental to structural and functional biological molecules thus contributing to PD pathogenesis (Schubert et al. 1995). Additionally, it was postulated that salsolinol's toxicity might result from the inhibition of complex I of the mitochondrial electron transport chain and subsequent oxidative stress (Betarbet et al. 2002). Salsolinol's toxicity has been extensively studied in various in vitro (Yoshikawa 1993; von Bohlen und Halbach et al. 2004; Olanow and Tatton 1999) and in vivo (Collins and Neafsey 2002) systems. In particular, in vivo and in vitro studies by Zhao et al. (2017) reported that salsolinol could alter rat brain endothelial cells' morphology, but also determine apoptosis and necrosis (Table 1). This cytotoxicity, disclosed in salsolinol-treated rat brain endothelial cells by decreased glutathione content (Fig. 6, panel a) and superoxide dismutase activity (Fig. 6, panel b), was significantly reversed following treatment with carnosine, a dipeptide endowed with antioxidant properties (Zhao et al. 2017). In addition, catalase activity in brain endothelial cells in salsolinol-treated rats was also significantly reduced (Zhao et al. 2017) suggesting that salsolinol may also potentially damage proteins by producing cross-links (Libondi et al. 1994; Zhao et al. 2017). Moreover, salsolinol has also been suggested to act as an endogenous neurotoxin, a molecule stable and difficult to clear out whose accumulation in SH-SY5Y cells may contribute to storage of toxins production of endogenous neurotoxins (Fig. 7) and overall oxidative stress that could result in neuronal cell death (Xie et al. 2014).

The potential contribution of salsolinol to the neurobiological effects of ethanol has been frequently proposed although not clearly recognized, still being a controversial matter of discussion since the discovery in the 1970s of its formation during ethanol metabolism. Interestingly, salsolinol was identified in high concentrations in the urine of human volunteers, following an alcoholic intoxication (Collins et al. 1979) as well as in the brain of rats treated with ethanol (Collins and Bigdeli 1975), making it likely that the oxidative stress induced by ethanol and by its main metabolite, acetaldehyde, may trigger a chronic impairment of DA neurons leading to neurodegeneration (Vaglini et al. 2013). As consistently reported in the recent years (Correa et al. 2012; Israel et al. 2017), ethanol is metabolized both peripherally and intracerebrally into acetaldehyde, and this latter compound can be converted into salsolinol which, in DA rich brain regions such as the posterior ventral tegmental area (pVTA), might be responsible of acting as first hit in the reinforcing effects of his parent compound (Peana et al. 2015, 2017; Israel et al. 2017), a feature that relates salsolinol to the neurobiological bases of alcohol addiction. Hipólito et al. (2012) and our research's group (Peana et al. 2016, 2017) have reviewed the evidence gathered on the production and detection of salsolinol, in distinctive brain areas, both under basal and after ethanol drinking conditions, and highlighted its presence in brain areas critical for the regulation of ethanol drinking behaviour. Indeed, a significant body of literature reports nowadays that salsolinol is a biologically active compound perhaps responsible also of mediating the rewarding actions of ethanol (Myers et al. 1985; Hipólito et al. 2009, 2012; Peana et al. 2017). This latter suggestion is strongly supported by the in vitro and in vivo findings that salsolinol increases mesencephalic DArgic neuronal excitability (Melis et al. 2015; Xie et al. 2013). Moreover, these cellular and behavioural effects of salsolinol take place through a mechanism involving opioid receptors (Matsuzawa et al. 2000; Hipólito et al. 2010; Xie et al. 2013). In this regard, Berríos-Cárcamo et al. (2017) recently reported that salsolinol stimulates μ-opioid receptors via the G protein-adenylate cyclase pathway and that this effect is fully blocked by the μ-opioid receptor antagonist, naltrexone (Berríos-Cárcamo et al. 2017). In addition, this study also showed that (S)-salsolinol is a more potent agonist in the rewarding effects of ethanol than the (R)-stereoisomer (Berríos-Cárcamo et al. 2017). Notably, the critical evaluation of the biological activity of salsolinol raises also some critical questions. Can salsolinol cross the blood-brain barrier? Is there a relationship between salsolinol in the periphery and

Table 1 Cytotoxic and apoptotic effects of the TIQs

Compound	Mechanism of toxicity	Apoptosis	Experimental setting of the study	References
1-Methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or salsolinol	Reduced activity of respiratory chain complex I	No	Ex vivo determinations in fetal rat brain	Mao et al. (2013)
	Dopamine oxidation ROS generation	No	Review	Wąsik and Antkiewicz-Michulak (2012)
	Inhibition of mitochondrial complex II Increased production of free radicals ROS generation Lipid peroxidation Glutathione reduction	Yes	Rat brain endothelial cells	Zhao et al. (2017)
	Mitochondrial damage ROS generation	No	SH-SY5Y cells (malondialdehyde levels)	Xie et al. (2014)
N-Methyl-1-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline or N-methyl-(R)-salsolinol	Activation of caspase 3	Yes	SH-SY5Y cells	Naoi et al. (2002)
	Postulated DAT-mediated transport and inhibition of mitochondrial respiration	No	Human embryonic kidney HEK-293 and mouse neuroblastoma Neuro-2A cells (cells survival)	Storch et al. (2002)
1-Benzyl-1,2,3,4-tetrahydroisoquinoline or 1BnTIQ	Reduction of ubiquitination of tubulin β	No	SH-SY5Y cells	Kohta et al. (2010)
	Inhibition of either or both DAT and COMT activities	No	Wistar rats	Wąsik et al. (2014)
	Postulated DAT-mediated transport and inhibition of mitochondrial respiration	No	Human embryonic kidney HEK-293 and mouse neuroblastoma Neuro-2A cells (cells survival)	Storch et al. (2002)
1-[(3,4-Dihydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol or norlaudanosoline or tetrahydropapaveroline	Inhibition of mitochondrial respiration ROS production Redox cycling	No	Review	Surh and Kim (2010)
	Inhibition of mitochondrial respiration	No	Mitochondrial fractions from C57BL mice brains	Morikawa et al. (1996)

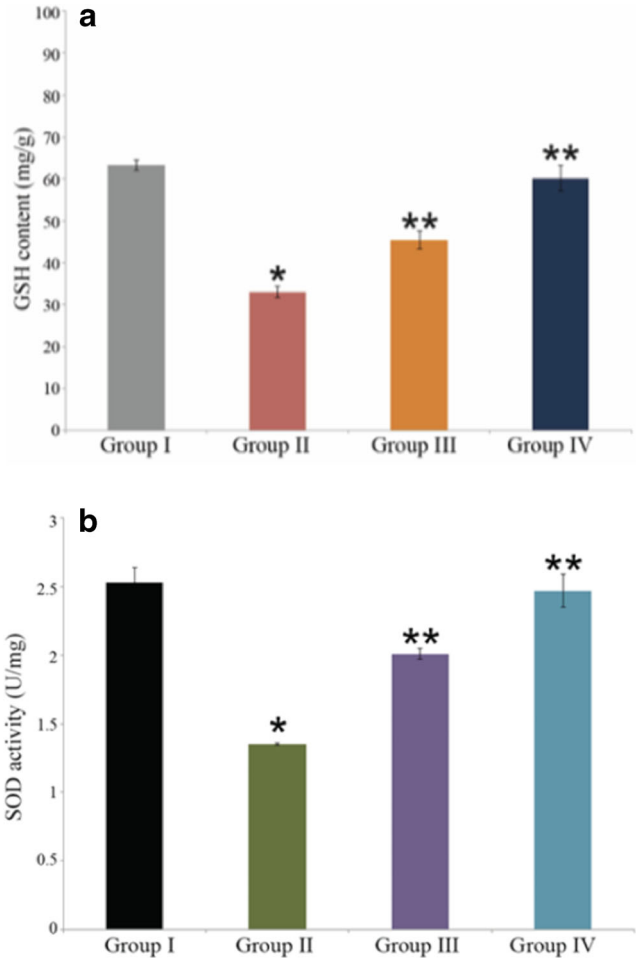

Fig. 6 **a** Protective effect of carnosine on salsolinol-reduced glutathione (GSH) content in the rat brain at 48 h. Results are presented as milligram/gram compared with the control. *$p < 0.05$ vs. group I (control); **$p < 0.05$ vs. group II (salsolinol 100 μg). Group III: carnosine 50 μg + salsolinol 50 μg; group IV: carnosine 100 μg + salsolinol 100 μg. Data are expressed as mean ± standard error of the mean. Reproduced with permission from Zhao et al. (2017). **b** Protective effect of carnosine on salsolinol-reduced superoxide dismutase (SOD) activity in the rat brain at 48 h. Results are presented as unit/gram compared with the control. *$p < 0.05$ vs. group I (control); **$p < 0.05$ vs. group II (salsolinol 100 μg). Group III: carnosine 50 μg + salsolinol 50 μg; group IV: carnosine 100 μg + salsolinol 100 μg. Data are expressed as mean ± standard error of the mean. Reproduced with permission from Zhao et al. (2017)

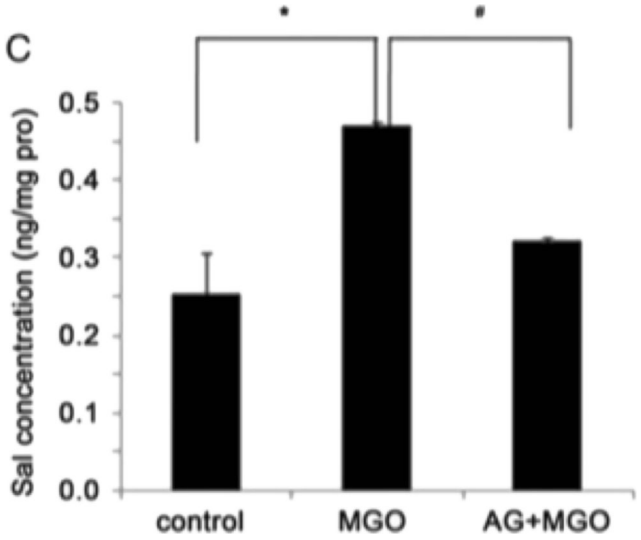

Fig. 7 Effect of salsolinol on aminoguanidine (AG)- and on methylglyoxal (MGO)-induced changes in DA. Cells were pre-incubated with AG for 1 h, then incubated for further 24 h in the presence of 600 μM MGO. Salsolinol was determined using LC-MS/MS. *$p < 0.05$ vs. control; #$p < 0.05$ vs. MGO. Reproduced with permission from Xie et al. (2014)

in the brain with respect to both neurotoxic and neurobehavioural effects? Interestingly, some evidence has shown that salsolinol may reach the brain by crossing the blood-brain barrier (Sjöquist and Magnuson 1980; Quintanilla et al. 2014). Nevertheless, some authors otherwise reported that salsolinol should not be able to cross the blood-brain barrier because its single peripheral administration did not result in measurable salsolinol levels in the brain (Origitano et al. 1981; Székács et al. 2007). On the other hand, peripheral administration of salsolinol can affect animal behaviour (Matsuzawa et al. 2000), suggesting that it could cross the blood-brain barrier. Although apparently resolved, this issue has long remained uncertain (Kurnik-Łucka et al. 2018; Origitano et al. 1981; Hipólito et al. 2009, 2012) and, until now, no study has established a mechanism through which exogenous salsolinol may cross the blood-brain barrier. In addition, as reviewed in details by Kurnik-Łucka et al. (2018), several aspects should be considered when trying to compare diverse findings of experiments aimed at establishing the ability of salsolinol to cross the blood-brain barrier: the commercial source, the dose, the stereoisomer, the route of administration as well as the experimental method, the animal species and strains employed in these tests.

Salsolinol is metabolized by the enzyme N-methyltransferase into N-methyl-salsolinol (Fig. 3), and finally is converted by MAO into the ion 1,2-dimethyl-6,7-dihydroxyisoquinolinium (Naoi et al. 2002, 2004). However, it can also be metabolized by COMT to form 6-methoxy- and 7-methoxy-(R/S)-salsolinol. Additional research is necessary to clarify several aspects of complex salsolinol (and others TIQs derivatives) pharmacokinetics.

Salsolinol Derivatives

N-Methyl-(R)-Salsolinol

Among salsolinol derivatives, N-methyl-(R)-salsolinol or N-methyl-1-methyl-1,2,3,4-tetrahydro-6,7-dihydroxy-isoquinoline appears possibly involved in the pathogenesis of PD (Naoi et al. 1996, 2002) perhaps by virtue of the selective cytotoxicity for *substantia nigra* DA neurons demonstrated in in vivo and in vitro studies by Naoi et al. (1996, 2002). In

particular, although the cytotoxicity of N-methyl-(R)-salsolinol to mesencephalic DA neurons has been questioned (Morikawa et al. 1998), this compound was reported to induce apoptosis by the activation of the apoptotic cascade initiated in mitochondria, as shown in Table 1 and Fig. 8 (Naoi et al. 2002). Surprisingly, the activity of a neutral (R)-salsolinol N-methyltransferase, a key enzyme in the biosynthesis of this toxin, has been found to be increased in the lymphocytes from parkinsonian patients, thus providing further support to the suggestion of its involvement in the pathogenesis of PD (Naoi et al. 1996; Maruyama et al. 2000). Nevertheless, the levels of N-methyl-(R)-salsolinol as well as those of its analogue 2-methyl-(R)-salsolinol in the cerebrospinal fluid of PD patients were found significantly higher than in healthy controls, a finding, however, not confirmed in other studies (Naoi et al. 2002). In agreement with this observation, Müller et al. (1999) showed that the same R- and S-salsolinol are not increased in cerebrospinal fluid of parkinsonian patients. Henceforward, it still remains obscure the significance of the levels of these TIQs and the significance of the presence, origin as well as of the mechanism of their production in vivo.

1-BnTIQ

As other TIQs, 1-BnTIQ (Fig. 3), besides existing in the environment, is detected in a number of foods, especially with a high β-phenethylamine content (Makino et al. 1988). 1-BnTIQ is derived from β-phenethylamine and is an endogenous neurotoxin that has been suggested as a factor responsible of causing PD (Kotake et al. 2014). This amine is described to cross the blood-brain barrier and to be present at higher concentrations in the cerebrospinal fluid of PD patients as compared with healthy controls (Kotake et al. 2014).

1-BnTIQ is reported to inhibit mitochondrial NADH-ubiquinone oxidoreductase (complex I) and to exert neurotoxicity eliciting PD-like behavioural abnormalities in monkeys and mice (Kotake et al. 2014). Likewise, these authors also reported that a 1-BnTIQ's first metabolite, 1-benzyl-3,4-dihydroisoquinoline (1-BnDIQ), is more toxic than its parent compound as assessed in cytotoxicity studies (Kotake et al. 2014). Furthermore, Wąsik et al. (2014) reported in in vitro and in vivo studies that both acute and chronic administrations of 1-BnTIQ to rats affect the behavioural and biochemical properties of L-DOPA suggesting that 1-BnTIQ's effects could be associated with the inhibition of DA membrane transporter (DAT) and/or of COMT activity in the brain. Additionally, this observation also raises the question that important endogenous levels of 1BnTIQ may represent a complicating risk factor in PD patients undergoing L-DOPA therapy (Wąsik et al. 2014).

Tetrahydropapaveroline or Norlaudanosoline

As mentioned above, TIQs significantly attracted the attention of neurochemists and pharmacologists when Davis and Walsh (1970) demonstrated that acetaldehyde could generate salsolinol in addition to the observation that also other aldehydes, such as dopaldehyde (another by-product of DA metabolism), could induce in vitro the conversion of [^{14}C]-DA into [^{14}C]-tetrahydropapaveroline or THP (Fig. 3). THP, also known as

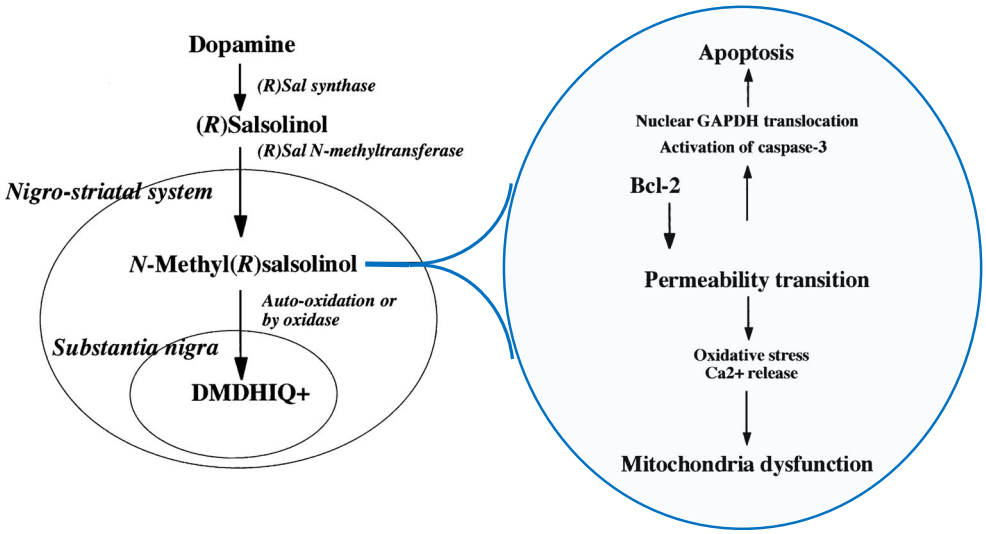

Fig. 8 Metabolism and cytotoxic mechanism of N-methyl-(R)-salsolinol in the brain. (R)-Salsolinol is enantioselectively synthesized from DA in situ by a synthase and N-methylation by a neutral N-methyltransferase induces the accumulation in striatal DA neurons. By retrograde axonal flow, N-methyl-(R)-salsolinol is transported to the substantia nigra and accumulates as the oxidized ion. N-methyl-(R)-salsolinol enantioselectively induces apoptosis in DA neurons through permeability transition, followed by decline in mitochondrial membrane potential and activation of following apoptotic cascade. Anti-apoptotic oncogene, Bcl-2 regulates the apoptotic signal transduction in mitochondria. Reproduced with permission from Naoi et al. (2002)

norlaudanosoline (Haber et al. 1997), is a putative DArgic neurotoxin that has been implicated in the pathology of Parkinson's disease and has been detected in the urine and brain of naïve rats treated with L-DOPA (Turner et al. 1974) as well as in the urine of parkinsonian patients on L-DOPA medication (Sourkes 1971; Sandler et al. 1973; Matsubara et al. 1992). Notably, whilst very little is reported in the literature about its possible neurotoxic effects, THP has been demonstrated to act as an endogenous and selective inhibitor of activated (phosphorylated) tyrosine hydroxylase, thus being able to suppress DA synthesis (Nowicki et al. 2015; Diamond and Yao 2015).

Grobe et al. (2010) also reported that THP is found in rodents' urine demonstrating that live mammals contain the enzymes to synthesize from THP, morphine, the presence of which in human and rodent tissue had been amply reviewed (Stefano et al. 2012). Interestingly, Sango et al. (2000) showed that (S)-THP may be enantioselectively synthesized in the human brain and may be an intermediate of the de novo synthesis of morphine analogues. Unfortunately, the nature of the enzymes that catalyse the transformation of THP into morphine is unknown as it is the identity of the underlying genes (Grobe et al. 2010). Moreover, THP has also been reported to bind to opiate receptor in rat brains (Pertel et al. 1980), suggesting that THP may interact with the endogenous opioidergic system (Weitz et al. 1987).

In addition, THP is considered to be involved in the pathogenesis of alcoholism and to act as a false neurotransmitter (Sango et al. 2000). Significant levels of THP have also been detected in the rat brain after intraperitoneal ethanol administration (Cashaw 1993). McCoy et al. (2003) studied the role of THP in the regulation of volitional ethanol intake concluding that THP could significantly facilitate it. Consequently, this endogenous alkaloid has been considered to account for the neurobehavioural abnormalities associated with alcoholism (Sango et al. 2000), although, to date, whether or not endogenously formed THP participates in the aetiology of abnormal ethanol intake and abuse remains fully to be determined (McCoy et al. 2003).

Overall, as reported by Collins (2004), the possible neurotoxic mechanisms of THP could be represented by an inhibition of mitochondrial respiration and serotonin production (see for review Surh and Kim 2010). Biochemical mechanisms underlying THP-induced neurotoxicity could be a consequence of a redox cycling and consequent cytotoxicity (necrosis or apoptosis, Table 1) due to ROS production as well as to reduction of ATP levels and DNA damage (Shin et al. 2004).

TIQs as Neuroprotectant

(S)-Norcoclaurine

Though not explicitly neuroprotective, (S)-norcoclaurine [(1S)-(1-(4-hydroxyphenyl)methyl-1,2,3,4-tetrahydroisoquinoline-6,7-diol)] (Fig. 4) is a biosynthetic TIQ alkaloid, derived from the condensation of 4-hydroxyphenyl-acetaldehyde, the oxidation product of tyrosine, and DA (Kennedy 2008). This condensation is postulated to be catalysed by the (S)-norcoclaurine synthase to generate tri-hydroxyisoquinoline (S)-norcoclaurine, which is the principal precursor of benzylisoquinoline alkaloids (Samanani and Facchini 2001; Vimolmangkang et al. 2016). In this regard, it has also been suggesting that (S)-norcoclaurine synthase plays a cooperative role between substrate-binding sites, suggesting that this enzyme could be regulatory or modulatory, playing a role in controlling the rate of pathway flux in benzylisoquinoline alkaloids biosynthesis (Samanani and Facchini 2001; Vimolmangkang et al. 2016). Notably, in spite of a critical structural variety, benzylisoquinoline alkaloids share the same biosynthetic origin, (S)-norcoclaurine, as first intermediate (Hagel and Facchini 2013). However, although several mechanisms were envisioned to explain the role of (S)-norcoclaurine synthase, its mechanism is still matter of debate. Interestingly, (S)-norcoclaurine is transformed into about 2500 identified benzoisoquinoline alkaloids, including the analgesic morphine, the antitussive noscapine, the muscle relaxant tubocurarine, the vasodilator papaverine and the antioxidant magnoflorine (Hagel and Facchini 2013), the latter being a by-product known to cross the blood-brain barrier and possess a marked central activity characterized by cognition-enhancing properties probably due to its ability of inhibiting acetylcholinesterase activity (Kukula-Koch et al. 2017).

Haber et al. (1997) reported that, in the rat brain, ethanol induces the formation of (S)-norcoclaurine, also recognized as a potential precursor of morphine in *Papaver somniferum* L. (Brochmann-Hanssen 1984).

Fascinatingly, in this regard, the observation that humans may excrete a small but steady amount of the benzylisoquinoline alkaloid, morphine, in the urine, has been a long-standing controversial issue whose origin has yet remained unclear as it has not been established whether it is to be considered of dietary or of metabolic origin.

Remarkably, important biological differences were discovered in the activity of (S)- and (R)-norcoclaurine enantiomers. Accordingly, a recent study in rat plasma has demonstrated that the (S)-enantiomer possesses a higher inhibitory potency than the (R)-enantiomer in platelet aggregation (Pyo et al. 2008). In agreement with this activity, (S)-norcoclaurine was reported to be more effective against lipopolysaccharide-induced intravascular coagulation as well as to increases the survival of mice with experimental endotoxemia (Yun-Choi et al. 2002; Park et al. 2006). Nevertheless, the low concentration of the (S)-norcoclaurine enantiomer obtainable from vegetables and the high-priced enantioselective synthesis of this TIQ really impedes its use in pharmacotherapy as well discussed by Ghirga et al. (2016).

Higenamine

Although not directly linked to ethanol, higenamine (1-[(4-hydroxyphenyl)methyl]-1,2,3,4-tetrahydroisoquinoline-6,7-diol) or dl-demethylcoclaurine (Fig. 4) is a compound which shares with other TIQs the same type of structure. Higenamine is the racemic form of norcoclaurine, present in several plant species (Ahmad et al. 2016). Interestingly, higenamine is a natural component of numerous traditional botanical remedies, dietary supplements or nutrients and is listed as an ingredient recommended for weight control and sports supplements (Cohen et al. 2019), thus making its consumption to result in violation of anti-doping regulations. In fact, due to its presumed on β2-receptors actions, higenamine is prohibited in sport at all times, being included, among β2-agonists, in the list of prohibited substances of the World Anti-Doping Agency (Grucza et al. 2017). Higenamine is a plant-based alkaloid, very popular in Chinese medicine, initially isolated from *Aconitum* (Kosuge and Yokota 1976), indeed identified as its active cardiotonic component. Accordingly, higenamine is well known due to its valuable therapeutic effects on different disorders like heart illnesses, disseminated intravascular coagulation, shock, arthritis, asthma, ischemia/reperfusion injuries, immunomodulatory effect and erectile dysfunction (for detailed review on higenamine, see Zhang et al. 2017). More recently, Wang et al. (2019a) have shown that higenamine could protect from the cerebral ischemia/reperfusion (I/R) injury via induction of axonal regeneration and repression of inflammatory reaction (neuro-inflammation), therefore proving the protective ability of higenamine in cerebral I/R injury (Wang et al. 2019a). Moreover, direct and indirect evidence indicates that higenamine acts in the sinoatrial node and ventricular myocytes through stimulation of β1 adrenergic receptor (Wang et al. 2019b). Based on these results, Wang et al. recommended this TIQ as valuable for the treatment of bradycardia (2019b).

On the other hand, Zhang et al. (2019) suggested that higenamine, directly binding to α1-adrenergic receptors, could be an innovative α1-adrenergic receptor antagonist. In particular, in different models of hypertension (normotension and spontaneous hypertension), higenamine was able to decrease the blood pressure (Zhang et al. 2019).

Overall, although the underlying mechanism of action of higenamine has not been clearly established, it has been suggested that it could have in addition a β_2 receptor agonist activity (Bai et al. 2008) and this effect could improve also glucose uptake in L6 cells (selected for high fusion potential and endogenous expression of GLUT4 in the myotube stage) (Kato et al. 2017). Generally, this mechanism of action could support the use of higenamine, as candidate agent for clinical diseases to treat some pathologies like diabetes and obesity whose β2 receptor-mediated beneficial effect are described (Kato et al. 2017), despite that its safety, tolerability and effectiveness are not yet, completely understood. The diverse pharmacological properties exhibited by higenamine indicate a wide spectrum of its therapeutic use as a consequence of some proposed mechanism(s) of action (Zhang et al. 2017). It is important to consider that some of the studies were small sample-sized and unreliable. Generally, there is a need for deeper investigation in the mechanisms of higenamine action, as well as for well-designed preclinical investigations and clinical trials to test the safety and clinical value of this TIQ (see the review by Zhang et al. 2017).

1-MeTIQ

The methyl derivative of TIQ, 1-MeTIQ (1-methyl-1,2,3,4-tetrahydroisoquinoline) (Fig. 4), is the simplest example of the un-substituted, non-catechol TIQ identified in plants and reported as an endogenous amine synthesized in human and animal brain (Abe et al. 2005). Interestingly, 1-MeTIQ presents in normal mouse brain with its highest concentrations in DAergic structures (mainly extrapyramidal system, substantia nigra and striatum) (Yamakawa and Ohta 1999). Kotake and collaborators (Kotake et al. 1995) have demonstrated that higenamine is able to prevent TIQ- and 1-BnTIQ-induced behavioural abnormalities (parkinsonism) in rodents (Kotake et al. 1995). It could be concluded that 1-MeTIQ occupies in the literature a privileged position because, as opposed to the majority of TIQs compounds, it is a substance with possible significant and wide spectrum of pharmacological actions in the central nervous system (Antkiewicz-Michaluk et al. 2014; Wąsik and Antkiewicz-Michaluk 2017).

Alzheimer's and Parkinson's diseases are neurodegenerative disorders where cerebral redox homeostasis plays an important role. A great deal of the experimental evidence demonstrates that oxidative stress is a principal reason of cell death and that an abnormal concentration of reactive oxygen and nitrogen species leads to the damage of a lot of lipids, proteins and also DNA. As reported by Antkiewicz-Michaluk and collaborators (Antkiewicz-Michaluk et al. 2014), 1-MeTIQ possesses neuroprotective actions, probably attributable to its ability to reduce oxidative stress (Antkiewicz-Michaluk et al. 2014; Wąsik and Antkiewicz-Michaluk 2017) by free radicals scavenging, prevention of cell membrane deterioration and glutamate-induced excitotoxicity inhibitory events (Antkiewicz-Michaluk et al. 2014; Chiba et al. 2015). Antkiewicz-Michaluk et al. (2014) also demonstrated that 1-MeTIQ through MAO inhibition might play an essential role in neuroprotection confirming the important role of catecholamines in the formation of TIQs (Antkiewicz-Michaluk et al. 2014). These researches have suggested that 1-MeTIQ possesses high affinity for brain tissue acting as partial DA agonist, reversibly reducing, both in vitro and in vivo, MAO-A and MAO-B activities, inhibiting more potently MAO-A than MAO-B (Patsenka and Antkiewicz-Michaluk 2004). Well in

agreement with this study, 1-MeTIQ completely antagonized clonidine-induced depression of monoaminergic systems restoring their levels to the control values. Therefore, 1-MeTIQ as an endogenous neuroprotective compound, with a different antidepressant-like activity in rodents, could be an effective antidepressant drug for future therapeutic use (Antkiewicz-Michaluk et al. 2017). Moreover, direct and indirect evidence indicates that 1-MeTIQ could be a potential antiparkinsonian drug on the basis of its ability to reduce MPTP-induced bradykinesia (Antkiewicz-Michaluk et al. 2014) and a potential drug useful for treating drug abuse, based on its ability to decrease craving as reported by Antkiewicz-Michaluk's research group (Antkiewicz-Michaluk 2002; Antkiewicz-Michaluk et al. 2014). A recent in vivo microdialysis investigation also demonstrated that multiple treatments with both endogenous amines, as TIQ and 1-MeTIQ, protect DAergic neurons against a 6-OHDA-induced reduction of DA release (Wąsik et al. 2018a). In addition, 1-MeTIQ was able to maintain physiological functions of striatal DA neurons damaged by a unilateral 6-OHDA lesion (Wąsik et al. 2018a). Well in agreement with this latter study, these authors have demonstrated, within vivo microdialysis as well as with ex vivo experiments, that repeated treatment of 1-MeTIQ protects DAergic neurons and prevents impairment of DA release in the rat brain, demonstrating the efficacy of 1-MeTIQ to maintain the physiological functions of DA neurons (Wąsik et al. 2018b).

Interestingly, (S)- and (R)-enantiomers of 1-MeTIQ, obtained at least partially through an enzymatic mechanism, have been identified (Fig. 4) in the mouse brain and in foods (Makino et al. 1990) with similar biological actions (Wąsik et al. 2012). More importantly, it was demonstrated that S-1MeTIQ, like the raceme but not the (R)-stereoisomer, prevents MAO-dependent DA oxidation in different brain areas. On the other hand, both (S)-1-MeTIQ and (R)-1-MeTIQ increase COMT-dependent O-methylation in the brain although the (R)-enantiomer is endowed with a lower neuroprotective efficacy (Wąsik et al. 2012).

N-Methyl-TIQ

Numerous studies have revealed the presence of N-methyl-TIQ in the human and rodent brain (see the review by Nagatsu 1997). The observation that this TIQ could be as reversible inhibitors of both MAO-A and MAO-B isoenzymes boosted a great interest in the area of endogenous substances that with such an interesting mechanism of action could act as neuroprotectants (Antkiewicz-Michaluk et al. 2003, 2004). This hypothesis is in agreement with other studies in which it demonstrated the lack of neurotoxicity of this and other TIQs in rodents (Lorenc-Koci et al. 2004; Perry et al. 1988). Yoshida and collaborators (Yoshida et al. 1993) described the effect of long-term treatment with N-methyl-TIQ on aged monkeys (Yoshida et al. 1993). In this regard, N-methyl-TIQ (Fig. 4), previously reported as non-catecholic endogenous TIQ, might act as MAO-A and MAO-B inhibitor (Patsenka and Antkiewicz-Michaluk 2004), probably acting as physiological regulator and feedback controller of brain monoamines, in particular of DA neurotransmission (Patsenka and Antkiewicz-Michaluk 2004).

Synthetic TIQ Derivatives

TIQ is a "*privileged scaffold*" structure, frequently found in nature. Therefore, the TIQ skeleton has nowadays been amply exploited as a model for the development of innovative drugs in spite of the fact that this class of compounds was firstly identified for its neurotoxicity, in particular, following the characterization of 1-MeTIQ as an endogenous parkinsonism-preventing agent in mammals. On this basis, a large number of synthetic TIQ derivatives have been synthetized and characterized. TIQs display a wide variety of potent biological activities, with evident promising success in the area of drug discovery against cancer and central nervous system diseases. They might also reveal to be promising candidates for several infectious illnesses, such as malaria, tuberculosis, HIV infection, HSV infection, leishmaniosis, etc. (see, for review, Singh and Shah 2017). Moreover, a large number of patents on various therapeutic activities of TIQs derivatives in the years between 2010 and 2015, also including several patents on specific TIQs of clinical importance, have been reviewed by Singh and Shah (2017). Likewise, these molecules might be developed as new class of drugs with various therapeutic activities probably also with unique mechanism(s) of action (Singh and Shah 2017).

Concluding Remarks

The experimental data gathered in this review allow for a comprehensive characterization of the differential activities of TIQs. On the basis of these reports, the following conclusions could be drawn: (a) TIQ derivatives are molecules similar in their chemical structure, normally present in plants and animals; (b) TIQs may be originated by condensation reactions between biogenic amines and aldehydes or α-keto acids; (c) several TIQs may be synthesized enzymatically whilst others may be formed in the body as by-products of other compounds; (d) ethanol can induce the formation of TIQs some of which might contribute to some of its neurological effects; (e) some TIQs are potent neurotoxic agents whilst others may exert neuroprotective and neurorestorative actions.

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