

LECTURES

1,2,3,4-Tetrahydroisoquinoline Derivatives as Endogenous Regulators of Dopaminergic Activity in CNS with Neuroprotective Action

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Several 1,2,3,4-tetrahydroisoquinoline (TIQs) derivatives present in the brain are endogenous. The most investigated of these compounds is 1-methyl-6,7,-dihydroxy-1,2,3,4-tetrahydroisoquinoline (salsolinol), which in mammalian brain is a product of enzymatic condensation of dopamine (DA) with acetaldehyde [13]. Salsolinol is present in the human brain, particularly in alcoholics, where the availability of acetaldehyde is higher. In a clinical study, we have found that the concentration of salsolinol in the cerebrospinal fluid of parkinsonian patients with advanced parkinsonism was significantly augmented and this increase was positively correlated with the degree of motor disability and dementia [5].

The suspicions that TIQs may be neurotoxic resulted from their similarity to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and ability to form tetrahydroisoquinolinium ions, analogous to 1-methyl-4-phenylpyridinium ion (MPP⁺), and in fact experimental parkinsonism was induced by TIQs in marmosets and rodents [15, 16]. While MPTP acts rapidly and produces irreversible neurotoxic changes after a single injection [6, 7], TIQs do not produce an immediate neurotoxicity. In the animal experiment, we have found that TIQs (1,2,3,4-tetrahydroisoquinoline, TIQ; 1-benzyl-1,2,3,4-tetrahydroisoquinoline, 1BnTIQ; and salsolinol) must be given at high doses repeatedly for at least three

weeks to induce rather weak neurotoxic effects [2, 4, 12]. Recently, the interest of researchers was attracted by two endogenous derivatives: 1-methyl-1,2,3,4-tetrahydroisoquinoline (1MeTIQ) and 1BnTIQ. 1MeTIQ was regarded as a neuroprotectant [18, 21], whereas 1BnTIQ was described as having neurotoxic properties [10, 11].

Apart from the propensity to form quaternary ions, the neurodegenerative effects of TIQs may be caused by the facilitation of DA metabolism and catabolism by N-oxidation. The oxidative MAO-dependent pathway of DA catabolism to form 3,4-dihydroxyphenylacetic acid (DOPAC) is associated with a subsequent production of hydrogen peroxide (H₂O₂), which in the presence of iron may be converted into a highly reactive •OH, which may play an important role in the progressive and selective loss of the nigrostriatal dopaminergic neurons that occurs in aging and in Parkinson's disease [8, 17]. On the other hand, the enhanced catabolism of DA through COMT-dependent O-methylation, leading to 3-methoxytyramine (3-MT) may be an important antioxidant defense mechanism [14].

The two tetrahydroisoquinolines, 1MeTIQ and 1BnTIQ, differently affect the DA metabolism and catabolism. 1MeTIQ does not change the DA level in any investigated structure (substantia nigra, striatum and nucleus accumbens) after a single injection, and even increases it after chronic treat-

ment. In contrast, a single dose of 1BnTIQ produces a dramatic fall of DA level in the striatum and nucleus accumbens with the increase in homovanillic acid (HVA) level, which indicates a massive release of DA from the nerve endings [2]. This may be the cause of neurotoxic properties of 1BnTIQ. The neuroprotective action on 1MeTIQ may be explained by its different action on both pathways of DA catabolism. 1MeTIQ strongly inhibits the DA MAO_B-dependent N-oxidation, and accelerates at least twice the COMT-dependent O-methylation [2]. Such an effect on DA catabolism may reduce the generation of free radicals in this process.

The different biochemical effects of 1MeTIQ and 1BnTIQ on DA catabolism suggest that only some endogenous TIQs, such as 1BnTIQ, may participate in the induction of degeneration of nigrostriatal DA neurons responsible for Parkinson's disease. Other compounds, such as 1MeTIQ, owing to their inhibitory effect on the N-oxidation catabolic pathway of DA, may protect the DA neurons against oxidative damage. Recently, we have found the protective effect of 1MeTIQ on rotenone-induced mortality and its neuroprotective effect against DA neurodegeneration after intracerebral injection of rotenone [1].

In contrast to a considerable body of data concerning the effects of chronic administration of TIQs, their immediate psychopharmacological effects were studied very little. In our study, we investigated their acute interference with dopaminergic system of the rat brain. In line with earlier results [9], we confirmed that TIQ compounds, TIQ, salsolinol, 1MeTIQ and 1BnTIQ administered to rats antagonized effectively the behavioral and biochemical action of DA agonists apomorphine and amphetamine [3,19]. Although many results point out at antidopaminergic effects of TIQs, several actions of these compounds are incompatible with the idea that they may have typical neuroleptic properties. Firstly, in contrast to neuroleptics, they do not produce profound sedation or catalepsy even at doses that produce distinctive rigidity [2, 12]. In contrast, typical neuroleptic haloperidol produces catalepsy at doses lower than those inducing rigidity [20]. They also do not potentiate the cataleptogenic action of haloperidol and show no synergism with neuroleptics in the action on DA metabolism. The neuroleptic-like effects are more difficult to be accounted for, as we have found that neither TIQ

nor salsolinol displaced ³H-spiroperone or ³HSCH₂₃₃₉₀ from their binding sites, indicating no neuroleptic-like affinity for DA receptors, however, they interfere with the agonist binding to DA receptors, which suggests that the compounds may suppress dopaminergic transmission at a site different from neuroleptic binding sites [3].

The above characteristics of TIQs and the fact, that they are present in the brain, and some of them may be synthesized from released DA (like salsolinol) make endogenous TIQs the ideal candidates for natural regulators of dopaminergic system, that would prevent its hyperactivity.

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CENTRAL DOPAMINE D₃ RECEPTOR ANTAGONISTS AS A POTENTIAL ANTIPSYCHOTIC DRUGS OF NEW GENERATION

Dedicated to Prof. Dr. Krystyna Kmiecik-Kołada
on the occasion of 35th anniversary of her scientific activity

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Dopamine (DA) receptors in the central nervous system attract significant scientific interest, due to their possible involvement in some psychotic and neurodegenerative disorders. Initially, DA receptors were divided into D₁ and D₂ subtypes, on the basis of their different activation of adenylate

cyclase [2]. DA D₁ and D₂ receptors have been implicated in the pathologies of Parkinson's disease and schizophrenia. A correlation exists between the average clinical dose of a neuroleptic and its affinity for brain DA receptors, as evaluated in studies of the binding inhibition of the D₂ antagonist ³H-spi-

perone. As long-term administration of typical neuroleptics (DA D₂ antagonists) to humans or to experimental animals can lead to development of extrapyramidal side effects (including Parkinsonian-like movement disorders, and tardive dyskinesia), a group of antipsychotic drugs, referred to as "atypical neuroleptics", has been developed. Recently, another DA receptor subtype, designated as D₃, has been cloned and categorized as a part of the DA-D₂-like receptor family [7]. D₃ has been shown to be localized primarily in the limbic brain structures, areas associated with cognitive, emotional and endocrine function. DA D₃ receptor is expressed both pre- and post- synaptically. Central DA D₄ receptor has also been cloned [8].

DA D₃ receptors raised great interest, because of their potential of being a target for new groups of antipsychotic and neuroleptic drugs [7]. Among these drugs, a few new DA D₃ agonists and antagonists were synthesized, and used as pharmacological tools for studying the role of D₃ receptors in the brain. Quinpirole and 7-OH-DPAT are regarded as D₃ agonists. The new antagonists of D₃ were also developed such as UH232, AJ76, DS-121, GR-103691, S-14297, SB-277011A, U-99194A, nafadotride and others. All of them exert some pharmacological action in mammals, being less or more selective for D₃ receptor than for D₂ receptor, and probably lower propensity to produce extrapyramidal side effects. Among them, the U-99194A [5] and nafadotride [6] were the focus of our study.

The effect of both antagonists on different parameters of rat's behavior (locomotion, yawning, oral activity, exploratory activity, catalepsy) and on biogenic amine levels (DA, DOPAC, HVA, 3-MT, 5-HT, 5-HIAA, NA) and on DA and 5-HT turnover in the striatum and hippocampus was examined, and compared with that of haloperidol (DA D₂ antagonist) or clozapine (DA D₄ antagonist). Beside the content of DA, DOPAC and HVA levels were measured in the neostriatal *in vivo* microdialysate and by *in vivo* voltametry after U-99194A challenge in rats. It was confirmed that U-99194A blocked DA D₃ receptor, but did not influence biogenic amine levels and release into microdialysate of the striatum, in opposition to haloperidol [1].

Similar effect was obtained by *in vivo* voltametry technique. The central pharmacological (behavioral and biochemical) profile of nafadotride action is closer to clozapine than to haloperidol. Preliminary results concerning U-99194A and nafadotride were presented elsewhere [3, 4].

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FROM BIOGENIC AMINES TO CYTOKINES IN THE BRAIN

Dedicated to Prof. Dr. Krystyna Kmiecik-Kołada
on the occasion of 35th anniversary of her scientific activity

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The “well of the river of psychopharmacology” rised, when the first chemical entities affecting human behavior were discovered. The almost simultaneous reports of the remarkable effects of minute amounts of lysergic acid diethylamide accidentally discovered by Hofmann [16] and the effects of chlorpromazine [5] and reserpine [3] inhibiting the agitation and anxiety in mentally-ill persons were main factors that catalyzed the explosive growth of psychopharmacology since 1954. This phenomenon was possible since the several hundred of behavioral and then biochemical techniques were invented.

About a decade earlier, the following very biologically active substances in the brain of experimental animals were found: norepinephrine (NE), 5-hydroxytryptamine, (5-HT), acetylcholine (Ach) and dopamine (DA). Since the phenomenon of peripheral neurotransmission was proven in these years, the abovementioned amines found in the brain except for DA were called cautiously “the putative neurotransmitters”. DA was considered at that time as a substance important only as one of the steps in the biosynthesis of NE. Numerous studies have proven that the following substances are the real neurotransmitters: NE [1], 5-HT [2], DA [4, 17] and Ach [6].

K. Kołada working in psychopharmacological group performed several experiments concerning the role of biogenic amines in the brain and mechanism of action of psychotropic drugs. It should be mentioned that she studied also the role of Ach in the central nervous system at the time when the most of scientists focused their attention on the research in the field of catecholamines and 5-HT.

Her main findings included providing support to the hypothesis that NE had regulatory role in the so-called ergotropic system and that 5-HT regulated so-called trophotropic system in the brain [12]. She proved that small (0.1–5 µg) but not higher doses of clonidine diminished very potently the concentration of total and free Ach, and that these small doses of clonidine were useful experi-

mental tool for stimulation of the central noradrenergic receptors [15].

Then K. Kołada described behavioral and biochemical effects of prostaglandins F_{2α} and E₁ [13], γ-aminobutyric acid [21], dibutyryl cyclic GMP [10] and 6-hydroxydopamine [11] in the central nervous system of mice or rats.

In 1989, K. Kołada published the monograph in which she summed up her studies on the central effects of LSD₂₅ [19]. The following important conclusions were presented in this paper:

- a. LSD affects the limbic area and mesostriatal system in different manner;
- b. It is an agonist of 5-HT receptors in the hippocampus, and ventral raphe;
- c. The lesion of serotonergic neurons of the hypothalamus endings elicits the hypersensitivity of serotonergic neurons;
- d. LSD affects the level of enkephalins in discrete brain areas. This psychodysleptic substance stimulates the central serotonergic neurons.

In the next studies, she discovered that the concentration of NE and 5-hydroxyindoleacetic acid was much higher in human gliomas as compared with non-malignant tumors [22], and she has found that in early phases of human cranial trauma, the rate of 5-HT turnover is evidently elevated [26]. Later on she has found that experimental brain concussion in rats alters significantly utilization of catecholamines and 5-HT in discrete brain areas [20].

In the meantime, the discovery of enkephalins took place [18] and the studies of the role of endogenous opioid peptides became a focus of great interest. The term of neuromodulators was coined [7] and K. Kołada switched her studies into this field. Using classical neuroleptics (chlorpromazine, thioridazine and haloperidol), she found that activation of dopaminergic neurons inhibited tonically the synthesis of enkephalins in the rat striatum [9].

During our studies on the antinociceptive effects of enkephalins, we discovered by chance that

four amino acid peptide (threonyl-lysyl-prolyl-arginine), tuftsin, a potent immunostimulator, had evident effects on the central nervous system, elicited analgesia, affected locomotor activity and increased blood pressure in rats, when injected intracerebroventricularly. These studies supported very strongly the hypothesis, not very popular at that time, that the evident link exists between the central nervous system and immune system [14].

Therefore, we started to work experimentally in the psychoimmunopharmacology. We observed that all types of opioid receptors mediate the immunological response of natural killer cells (NK) and macrophages, and that neuroleptics: chlorpromazine, haloperidol and sulphiride increased the activity of NK and macrophages in rats [8]. Recently, we have shown that neuroleptics normalize increased release of interleukin-1 β and tumor necrosis factor- α from monocytes in schizophrenics [23]. These data incited our interest into the psychoimmunopharmacological studies of neuroglia.

In our newest publication, we have found that flupentixol and trifluoperidol reduce secretion of tumor necrosis factor- α and nitric oxide by the rat microglial cells. These results suggest that these drugs may be used in the treatment of the central nervous system diseases associated with excessive TNF α and nitric oxide release, e.g. in inflammatory brain diseases [25]. On the other hand, we described that enkephalins increased interleukin-1 β release in mixed glial cultures [24]. Five years ago, inflammatory hypothesis of atherosclerosis was introduced. We published few papers in which we have shown that statins, and fibrates, which are broadly used as antihyperlipidemic drugs, potently suppress the release of cytokines from the cultured immunologically active cells from patients with atherosclerosis. These fascinating results supporting inflammatory hypothesis of atherosclerosis are beyond the scope of attention of psychopharmacologists.

Over 35 years of the presented above studies, K. Kołada accompanied our group with great determination, dedication to science and the great warm-heartedness to all of us.

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PRIMING AS A PROCESS FOR PRODUCING DOPAMINE D₂ RECEPTOR SUPERSENSITIZATION: RELEVANCE IN PSYCHIATRIC DISORDERS

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Because of their prominent position in several psychiatric and neurodegenerative disorders, dopamine (DA) neuronal circuits in brain have been intensively studied over the past 20 years. The most common of DA-associated neurodegenerative disorders is Parkinson's disease, while the most common of DA-associated psychiatric disorders is schizophrenia. In modeling either type disorder, DA receptors occupy an important position, as adaptations in these recognition sites are often thought to account for much of the symptomatology or represent a target for medical therapies.

There are two families of DA receptors, D₁ subtype (D₁, D₅) and D₂ subtype (D₂, D₃, D₄). Following the destruction of DA neurons or DA innervation, these families of receptors undergo changes in either number or sensitivity. There have been many papers describing changes in numbers of DA receptors after DA denervation. However, the focus in this brief paper is on the phenomenon known as D₂ receptor supersensitization – but generally in the absence of DA denervation. Some aspects of this topic have been partly reviewed elsewhere [21, 28, 29].

Breese et al. discovered that ontogenetic destruction of nigrostriatal dopaminergic neurons is

associated with prominent DA D₁ receptor supersensitization, as indicated by enhanced behavioral responses to agonists. However, although enhanced effects were seen after the first dose of L-dihydroxyphenylalanine (L-DOPA), enhanced effects to specific DA D₁ agonists were observed only after the third treatment with the agonist. This delayed or latent supersensitivity that was unmasked by repeated treatments has become known as a priming phenomenon [2–5, 12]. The induction of D₁ receptor supersensitivity can be produced by either DA D₁ agonists (homologous priming) or DA D₂ agonists (heterologous priming). An even greater enhancement of priming is produced by repeated treatments with a D₁ agonist during the first 4 weeks of postnatal development [16, 18, 19]. However, DA D₂ receptors do not become similarly primed in the DA-denervated models [12].

When rats were treated daily during the first 4 weeks of postnatal development with a DA D₁ receptor antagonist, the number (i.e. B_{max}) of striatal DA D₁ receptors was reduced in adulthood [30, 36]. Likewise, when rats were treated daily during the first 4 weeks of postnatal development with a DA D₂ receptor antagonist, the number (i.e. B_{max}) of striatal DA D₂ receptors was reduced in adult-

hood [31, 37]. As a continuation of the above series of studies, we observed that daily D₁ agonist treatments during postnatal development did not have an appreciable effect on D₁ receptor development in rat striatum, when the DA system was not lesioned [18, 19]. However, for several behaviors including vacuous chewing, there was overt behavioral supersensitivity to the first dose of a DA D₁ agonist in rats in which the nigrostriatal DA system had been destroyed in early postnatal ontogeny [15, 17, 25].

In an attempt to better understand the mechanisms underlying DA receptor supersensitivity, a series of studies was conducted with DA D₂ agonist treatments. When intact rats were treated repeatedly from birth with a DA D₂ agonist, there was stimulation of eating (pelleted rat chow) and motor activity, first observed within minutes of the daily dose of D₂ agonist, quinpirole (3.0 mg/kg/day). At postnatal day 19 (PD 19), quinpirole induced a 'darting'-like effect [27]. Over the next 10 days, daily quinpirole treatments were associated with long periods of rearing, paw treading, and vertical jumping, all occurring in the first several hours after the single daily quinpirole treatment [26].

Subsequently, we observed that a daily dose of quinpirole produced prominent yawning activity [22] even when the daily quinpirole dose was as low as 50 µg/kg/day and continuous only for 11 days at different ontogenetic periods of development: PD 0-PD 11, PD 12-PD 22, or PD 23-PD 33 [8, 24]. These rats also displayed enhanced quinpirole analgesia in a hot-plate test, with quinpirole analgesia additive to morphine analgesia but blocked by the DA D₂ receptor antagonist spiperone [23].

Enhanced quinpirole responses were also observed in rats in which brain serotonin (5-HT) innervation was reduced by neonatal treatment with the 5-HT neurotoxin 5,7-dihydroxytryptamine [7, 9]. There was an indication that some [7, 27] but not all [7, 9] of the quinpirole-primed responses were present even in rats in which the striatum was largely DA-denervated by neonatal 6-hydroxydopamine (6-OHDA) treatment. In contrast to the effects of quinpirole, the largely DA D₃ agonist (±)-2-(dipropylamino)-7-hydroxy-1,2,3,4-tetrahydronaphthalene (7-hydroxy-dipropylaminotetralin; 7-OH-DPAT) did not produce enhanced behavioral responses in rats that were primed with daily doses of either quinpirole or 7-OH-DPAT [34, 35], although release of dihydroxyphenylacetic acid

(DOPAC) was increased in the striatum of female rats acutely treated with either 7-OH-DPAT or quinpirole [35].

Several studies have now shown that quinpirole produces sensitization to D₂ agonists, even when quinpirole treatments are started in adulthood and administered at intervals of a week or more [10, 13, 14], and that prominent locomotor sensitization occurs to quinpirole [32, 40, 43, 44]. Also, conditioned avoidance learning [11] and skilled reaching [6] is enhanced in quinpirole-primed rats, although cognitive deficits (Morrison water task) are prominent [6] in the quinpirole-primed rats.

When rats primed with quinpirole as neonates were challenged in adulthood with an acute dose of amphetamine (1.0 mg/kg *ip*), there was a 5-fold increase in DA efflux in the striatum. However, acute quinpirole challenge had little effect on striatal DA efflux when compared to controls [33]. Because behavioral sensitization to amphetamine is thought to be mediated in part by subsensitization of DA D₂ autoreceptors in the ventral tegmental nucleus [1, 20, 38], the latter effect may represent one of the major outcomes of quinpirole priming [33].

Because quinpirole-primed rats become engaged in repeating behaviors, such rats have been proposed as a model of obsessive-compulsive disorder (OCD) [39, 41, 42, 45, 46]. Moreover, nicotine which attenuates quinpirole enhancement in quinpirole-primed rats, is also effective in treating OCD and the animal model of OCD [45, 46]. Quinpirole-primed rats have also been promoted as a suitable model for psychosis or schizophrenia [6].

In summary, it is now recognized that DA D₂ receptors can be primed by repeated treatments with the DA D₂ agonist quinpirole. This effect is most prominent when DA innervation in brain is fully intact. Moreover, the effect can be produced by

- quinpirole treatments during early postnatal ontogeny, or by
- quinpirole treatments during adulthood, and
- with a very low dose of quinpirole.

Some enhanced quinpirole effects (i.e. rearing and vertical jumping) persist even when the striatum is largely DA-denervated. Quinpirole enhancement can be produced without priming, when 5-HT nerves are damaged. Despite the prominent behavioral actions of quinpirole in quinpirole-primed rats, the underlying mechanism for this phenomenon remains unknown. However, because amphetamine effects are prominent in quinpirole-primed

rats, and because subsensitization of DA D₂ autoreceptors is associated with behavioral sensitization to amphetamine, it is conceivable that the phenomenon known as receptor *supersensitivity* is more accurately a receptor *subsensitivity*, specifically of D₂ autoreceptors in the ventral tegmental nucleus. Despite continued experimentation to define the phenomenon known as receptor supersensitivity, quinpirole-primed rats represent a useful model for OCD, psychosis, and perhaps still-to-be defined psychiatric conditions.

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NEUROTRANSMITTER MECHANISMS IN THE MODEL OF KINDLED SEIZURES

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INTRODUCTION

The kindling of seizures is recognized as the best animal model of temporal lobe epilepsy [1, 4, 5]. Kindling is usually evoked by a repeated application of an initially subconvulsive electrical stimulation to such brain structures as amygdala, hippocampus, piriform cortex, gradually leading to generalized seizures. Similar effect may be obtained by repeated systemic injection of a proconvulsive chemical substance like pentetotetrazole (PTZ), at subconvulsive dose [2, 4]. Pretreatment with PTZ, besides lowering the convulsion threshold, leads to the histological changes in the brain structures, similar to those observed in epileptic patients. Histological changes involve degenerative processes in both glial tissue and neurons in the hippocampus along with the piriform cortex and amygdala [3].

Kindling of seizures is a complex process involving not only excitatory amino acid and GABAergic systems but also the central monoaminergic innervation. PTZ is an uncompetitive GABA antagonist which secondarily to disinhibition of excitatory processes in the brain modulates also the activity of monoaminergic systems. The role of monoamines in epileptogenesis is well documented. The particularly important role is ascribed to serotonin (5-HT) and limbic hippocampal serotonergic innervation. Some antiepileptic drugs (e.g. carbamazepine, zonisamide) can modify serotonergic activity, and the serotonergic system may be directly involved in the mechanism of action of these drugs. The brain serotonergic system is implicated in the mechanisms regulating various types of experimentally induced seizures. In the experiments with *in vivo* microdialysis, a low pre-kindling 5-HT concentration correlated with an increased seizure susceptibility [4]. A spontaneous and experimentally induced depletion of noradrenaline (NA), dopamine (DA) and 5-HT has been related to the onset and development of many seizure disorders. On the other hand, several experimental procedures designed to increase monoaminergic activity have demonstrated their antiepileptic properties. How-

ever, the exact site of interaction between limbic 5-HT and the sensitization effect of PTZ treatment is not known.

Convulsions have both short- and long-term effects on animal behavior and brain neurotransmitter system activity. Chemically and electrically induced seizures release neurotransmitters in the brain, leading to the transient post-ictal depletion in the indoleamine and catecholamine stores [4]. Simultaneously, kindling is followed by some behavioral effects like antinociception, decreased learning and memory, and anxiety-like behavior. However, no simple correlation exists between the changes in the release of NA and 5-HT and the effects of PTZ on behavior. The available data indicate that PTZ-induced behavioral changes may be due to the modification in the synthesis and release of monoamines, caused by altered synaptic regulatory processes, which can occur as a result of neuronal loss, gliosis or neuronal sprouting [3].

METHODS

The aim of the presented study was to perform a detailed analysis of some behavioral and biochemical effects of PTZ-induced kindling of seizures in rats. The behavior of fully kindled animals was analyzed in several models of anxiety-like reactions, including the open field test, the Vogel test, the ultrasonic vocalization test, and the contextual fear conditioning. Moreover, the effects of kindling on monoamine levels and turnover rates were examined in some brain areas. Finally, a correlative analysis between the behavioral and biochemical changes was performed. It is considered that such comparison could provide us with new important information. This may also help to better characterize the mechanisms of central effects of kindling, and lead to better understanding of emotional disturbances observed in epileptic patients.

We also examined [³H]-citalopram binding in the rat brain structures, and the neurodegenerative effects in the hippocampal formation using autora-

diographic and immunohistochemical methods in order to answer the question whether PTZ kindling-induced degenerative changes in the limbic system involve also a local 5-HT innervation. This might be an important element of a process of seizure sensitization. To achieve this goal we used histochemical, immunohistochemical and autoradiographic methods. [³H]-citalopram, one of the 5-HT reuptake inhibitors, was used to mark serotonergic terminals, as it is the most selective 5-HT transporter blocker.

RESULTS and DISCUSSION

The repeated administration of PTZ (35 mg/kg, *ip*) evoked kindled seizures in rats (stage 4 or 5 of clonic-tonic convulsions – maximum). PTZ kindling caused selective changes in the rat emotional behavior, present in some models of anxiety only (a decreased freezing time in the conditioned freezing test and a decreased spontaneous and averively conditioned aversive ultrasonic vocalization). Simultaneously, PTZ kindling decreased the concentration of HVA and 5-HIAA in the prefrontal cortex, decreased the DA (HVA/DA ratio) turnover rate in the striatum, and inhibited the 5-HT metabolism (5-HIAA/5-HT ratio) in the hippocampus and the prefrontal cortex. Correlations between DA or 5-HT regional metabolic rates in brain structures and animal behavior were either abolished or reversed in PTZ-kindled animals. It is concluded that both DA and 5-HT systems contribute to the emotional effects of PTZ-induced kindling of seizures. The hypothesis is put forward that PTZ kindling-induced inhibition of the serotonergic innervation may lead to the compensatory increase in 5-HT_{1A} receptors in the dentate gyrus of the hip-

campus, thus, evoking the anxiolytic-like changes in animal behavior.

Moreover, a statistically significant and selective reduction in the binding of [³H]-citalopram was found in the CA3 field of the hippocampus ($p = 0.009$), and a similar tendency, close to the significance level, was observed in the dentate gyrus ($p = 0.05$), in the PTZ model. This effect was accompanied by a loss of neurons and activation of microglia in the hippocampal formation. The present data suggest the important role for CA3- serotonergic innervation in PTZ-induced kindling of seizures.

Altogether, the presented data show that the PTZ model of kindling is a suitable tool to study the central mechanisms underlying the kindled seizures.

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DOPAMINE AND GLUTAMATE DYSFUNCTIONS IN SCHIZOPHRENIA: ROLE OF THE DOPAMINE D₃ RECEPTOR

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The classical dopamine hypothesis of schizophrenia owed its birth to the serendipitous discovery in the early 1950s of the potent antipsychotic

properties of chlorpromazine [5]. The therapeutic effect of chlorpromazine and other antipsychotic drugs, was attributed a decade later to the ability of

these drugs to increase dopamine metabolites in the brain, in rough proportion to their clinical efficacy [3]. It was subsequently hypothesized that alterations of dopamine metabolism by antipsychotic drugs resulted from blockade of dopamine receptor, at that time unidentified, and that psychotic symptoms were elicited by overstimulation of these receptors. The hypothesis postulating a hyperactivity of dopamine systems in schizophrenia received a strong support from the observation that dopamine-releasing agents, such as amphetamine, were able to induce psychotic symptoms in abusers, and to exacerbate these symptoms in schizophrenic patients [2]. The subsequent discovery that therapeutic potencies of antipsychotic drugs were correlated with their affinity for certain brain dopamine receptors [4, 16] has added arguable value to the hypothesis.

Since those times, the dopamine hypothesis of schizophrenia has received additional supports. The direct evidence for a primary increase in dopamine activity, e.g. increase in dopamine receptor expression or dopamine metabolites in body fluids, has been weak at the beginning. Nevertheless, more recent positron emission tomography analyses have shown an enhancement of amphetamine-induced dopamine release in schizophrenic patients, strongly suggesting an endogenous dopamine hypersensitivity state in schizophrenia [13]. Moreover, the discovery of five distinct genes coding for dopamine receptors [19] has rejuvenated hopes for a better comprehension of the pathophysiology of schizophrenia and for better treatments of this disorder.

It is usual to classify the receptor subtypes into two subfamilies, based on the gene structure, primary sequence homology and intracellular signaling. The first subfamily includes D_1 and D_5 receptors, of which the genes are intronless and which are positively coupled to adenylyl cyclase. The second includes D_2 , D_3 and D_4 receptors, which are encoded by genes with introns that can lead to splicing variants (D_{2S} and D_{2L}), and inhibit cyclic AMP formation. Since its discovery [18], the D_3 receptor has attracted particular attention. Firstly, all antipsychotic drugs bind with high affinity to the D_3 receptor. Moreover, neither D_3 receptor up-regulation nor tolerance to D_3 receptor blockade occurs upon repeated antipsychotic drug administration. Secondly, D_3 receptors are localized in brain areas, namely the mesolimbic dopaminergic system originating from the ventral tegmental area and projecting to the nucleus accumbens and cerebral cortex, which have been implicated in neural

circuits believed to display defective functioning in schizophrenia [2]. Thirdly, a post-mortem study has shown a D_3 receptor overexpression in the brain of drug-free schizophrenic patients, whereas D_3 receptor expression was normal in subjects under antipsychotic drug treatment [8], suggesting that antipsychotic drugs normalize D_3 receptor expression. Fourthly, D_3 receptor overexpression in animals has been involved in sensitization to indirect dopamine agonists [1, 14], a clinical feature of schizophrenia [10]. Finally, a meta-analysis indicates a genetic association of a polymorphism in the D_3 receptor gene with a small, but significant enhancement of the vulnerability to schizophrenia [6].

However, the dopamine hypothesis has been progressively challenged in view of the relative lack of clinical efficacy of antipsychotic drugs to improve affective defects and cognitive impairments, which often mark the chronic evolution of the disease. Hence, a role of other neurotransmitters in schizophrenia has been proposed, notably glutamate. The glutamate hypothesis of schizophrenia has been elaborated from the following clinical observations. Phencyclidine (PCP), a non-competitive antagonist at the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor, is an anesthetic agent that has psychotomimetic properties in man [11]. PCP produces schizophrenic-like symptoms in healthy volunteers or abusers [17, 12], and precipitates psychosis in schizophrenic patients [9]. On the contrary, drugs facilitating glutamate neurotransmission by acting at the glycine accessory site of the NMDA receptor, such as D-cycloserine, improve schizophrenia and enhance the efficacy of antipsychotic drugs, notably against the negative symptoms of the disease [7]. These observations led to the proposal that schizophrenia may result from glutamate deficiency. However, the relationships at the molecular level between dopaminergic and glutamatergic systems in schizophrenia are not understood.

In animals, PCP or MK-801, another non-competitive NMDA receptor antagonist (Wong et al., 1986), elicit behavioral abnormalities, including hyperactivity, disruption of sensorimotor gating and social deficit that are circumvented by antipsychotic drugs, particularly of the atypical type [12]. We have investigated whether the corrective effects of antipsychotic drugs on MK-801-induced hyperactivity involve D_3 receptor blockade. For this purpose, we compared the effects of either typical or atypical antipsychotic drugs, to those produced by

D₃ receptor-selective agents in wild-type and D₃ receptor knockout mice. We found that hyperactivity produced by low doses of MK-801 was potently and completely inhibited by haloperidol, clozapine, nafadotride, a D₃ receptor-preferring antagonist, or BP 897, a highly D₃ receptor-selective partial agonist [15], with ED₅₀ ranging from 0.05 to 0.2 mg/kg. Unlike the other agents, haloperidol also inhibited spontaneous locomotor activity at the same doses. That the D₃ receptor mediated the effects of MK-801 was confirmed by the dramatic decrease in MK-801-induced hyperactivity in D₃ receptor knockout mice. The inhibitory effects of nafadotride and BP 897 were completely suppressed, whereas those of haloperidol and clozapine were, at most, partially suppressed. These results indicate that the MK-801-induced hyperactivity remaining in D₃ receptor knockout mice was not D₃ receptor-dependent and that the effects of haloperidol probably involved interactions with other receptors.

Our results show that activation of the D₃ receptor is a major mechanism underlying locomotor effects of NMDA receptor blockers at low doses. A locomotor stimulatory role of D₃ receptors has already been suggested for mediating dopamine agonist-induced rotations in hemiparkinsonian rats [1] and cocaine-conditioned hyperactivity [14]. The D₃ receptor, however, seems to take only a minor part in the maintenance of spontaneous locomotor activity, which is not affected by D₃ receptor-selective agents, suggesting that D₃ receptors mediating locomotion are largely unoccupied by dopamine under basal conditions. Blockade of the D₃ receptor produces an effect very similar to that produced by antipsychotics on MK-801-induced hyperactivity, which, therefore, supports the growing evidence suggesting that D₃ receptor blockers might have antipsychotic properties. They also suggest that the D₃ receptor may be the intermediate linking glutamate and dopamine dysfunctions in schizophrenia.

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NEW PERSPECTIVES IN TREATMENT THERAPY OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD), dementia appearing usually after the age of 65, is one of the most important health hazards in the 21st century. The number of afflicted is steadily growing, presently reaching 16 million in the world. Approximately 50% of the population over 90 is affected.

The cause of AD is most probably an unfortunate combination of adverse genetic predispositions and environmental factors. The genetic influence is particularly visible in the population of patients in which the symptoms of AD appeared early, before the age of 60, and presently we know several mutations linked to the early form of AD. However, the early form is rare, its prevalence in the total population of suffering from AD is around 5%.

AD is a tragic blow to the patient, whose personality is slowly disintegrating, causing progressing deterioration in coping with the demands of external world, and also for the family and caregivers, who have to stand, at the beginning, psychotic reactions of various types, such as paranoia, verbal and physical aggression, groundless accusations, escapes, accidents due to deficits in everyday functioning (e.g. leaving the entrance door opened, fires, gas explosions), and later on to care about the person who completely lost the ability to perform basal functions such as eating, defecation etc. In addition, AD is not only psychic, but also a financial burden. The yearly cost linked with AD in the USA only is estimated at \$80–100 billion.

The direct cause of AD is accelerated apoptosis of some populations of neurons that begins in the fourth decade of life and crosses the threshold permitting proper cognitive functioning usually in the middle of seventh decade. Those changes, similarly as the whole course of disease, are progressive and lead invariably to total dementia and death.

The exact molecular ground of changes bringing out AD is still a matter of conjecture, but the main cause is undoubtedly generation of specific forms of proteins with high preponderance to form pathological aggregates. In AD such proteinaceous forms are β -amyloid ($A\beta$) which forms senile pla-

ques, and hyperphosphorylated tau proteins that produce neurofibrillary tangles.

Most of researchers devote particular attention to $A\beta$. The protein is formed from a ubiquitous large amyloid precursor protein (APP). APP is a transmembrane protein (crossing both cellular membrane and membranes of intracellular organelles) which in all cells of the body is processed by two enzymes: α - and γ -secretase. The product of the action of α -secretase, which cuts APP from the extramembrane side close to the membrane, is a soluble protein sAPP, which seems to play a protective role for the cell. The remaining part of APP, anchored in the membrane, is cut within the membrane by γ -secretase (it is still not explained how this hydrolase may act in extremely hydrophobic environment), yielding intracellular amyloid domain (ICAD) that is believed to play a role of a transcription factor controlling the genes regulating the intracellular calcium signaling. It should be noted that γ -secretase is a promiscuous enzyme, attacking several transmembrane proteins, and is not very precise in finding the place of hydrolytic attack, as its main component, presenilins, exist in several mutations.

In the brain (and also in some peripheral tissues), APP is also processed by another enzyme, β -secretase, which cuts the precursor from the extramembrane side, but further from the membrane, so that after processing by γ -secretase the remaining fragment of APP, anchored in the membrane and sticking to the outside, is a protein consisting of 39–43 amino acids (depending of the action of γ -secretase). This protein is $A\beta$. The most frequent form of $A\beta$ are $A\beta_{40}$ and $A\beta_{42}$. While $A\beta_{40}$ is relatively benign, $A\beta_{42}$ has great preponderance to initiate formation of insoluble $A\beta$ deposits that are highly neurotoxic, as they induce inflammatory processes and release of free oxygen radicals that kill the neighboring neurons.

The neurobiological cause of AD is a deficit in signaling in the forebrain cholinergic system responsible for the processes of memory and attention (leading to loss of cognitive functions) and se-

rotonergic and noradrenergic neurons in the brain stem (leading to psychotic manifestations, aggression and depression). The deficit in neurotransmission is caused by the loss of appropriate neuronal populations caused by neurotoxic effect of senile plaques on the neighboring neurons and by blockade of intraneuronal transport by neurofibrillary tangles.

Presently, we do not know any drug reverting the progress of AD, or even effectively stopping it. The only available are drugs that slow down the increase in the dementia symptoms by supporting the fading transmission of signals in cholinergic neurons. Those drugs are cholinesterase inhibitors. Two of the drugs marketed presently, donepezil (Aricept) and galantamine (Reminyl), are selective inhibitors of acetylcholine esterase, the enzyme localized in cholinergic synapses. The third drug, rivastigmine (Exelon), has a wider spectrum of action, as it blocks also extraneuronal butyrylcholinesterase, which is present, among others, in senile plaques, and is believed to be involved in their generation. The introduction of these drugs, particularly in the early and middle stages of AD, may considerably prolong the period of functional autonomy of the patients. Other drugs that are used in AD are those preventing the psychotic symptoms. The drugs of choice are modern atypical neuroleptics, e.g. risperidone (Rispolept) and SSRI antidepressants, e.g. citalopram (Cipramil).

The search for the drugs acting causally on AD was accelerated by introduction of the animal model of AD – the transgenic mice that produce excessive amounts of human APP and speedily developing the neuromorphological and cognitive symptoms resembling those appearing in human AD. Several very promising results were obtained, but as for now they are not well transposed to the clinic.

The main line of research is looking for drugs inhibiting the formation of A β from APP. Both the inhibitors of β - and γ -secretases and the activators of α -secretase are considered. Another line is the search for drugs that prevent formation of A β deposits from the A β already formed. As heavy metals, such as copper or zinc, are important participants in the process of A β aggregation, the chelating compounds are tested. In the animal model, very promising results were obtained with a well-known antibiotic, clioquinol, which is a zinc- and copper-chelating agent.

Another tactical approach is a search for the compounds that would disrupt already formed A β

deposits. The formation of a deposit involves the change in the protein conformation from soluble α -helix into insoluble β -sheet. Several small peptides were devised that are built into the β -sheet structure and destabilize it, and it is hoped that such β -breakers may be useful in decomposition of senile plaques in humans.

Great hopes were aroused recently by amyloid vaccines. In mice vaccinated with A β , anti-A β antibodies were formed. On one hand, those antibodies bound to the circulating A β , formed complexes too large to cross the blood-brain barrier which prevented penetration of extracerebral A β into the brain. On the other hand, anti-A β antibodies activated cerebral macrophages that destroyed the A β deposits. Although in transgenic mice the vaccines were very efficient, the results in humans were disappointing.

Besides the fighting of A β , a considerable effort is devoted to prevent formation of fibrillary tangles. As they are formed due to hyperphosphorylation of tau proteins resulting from a shift between phosphorylation and dephosphorylation processes, the search for inhibitors of kinases, particularly CDK-5 and GSK-3 β and activators of phosphatases, particularly PP2A, is conducted.

A group of researches assumes that the main cause of neuronal death in AD are neuroinflammatory processes, induced by senile plaques. Thus, several anti-inflammatory agents from the group of NSAIDs are tested. The early results suggest that COX-1, and not COX-2 inhibitors may be effective, and this is not a fortunate situation, as the risk-benefit ratio must be assessed due to the adverse effects of COX-1 inhibitors on gastric mucosa. As neuroinflammation leads to generation of free radicals, the use of antioxidants, such as vitamin E or selegiline (Jumax) is advised.

High cholesterol level is also a factor facilitating the formation of A β deposits. Epidemiological studies have revealed that in the population of patients treated with statins the incidence of AD is low. Studies with statins, such as pravastatin, atorvastatin and simvastatin, suggest that their use is associated with a lower prevalence of dementia and has a positive impact on the progression of cognitive impairment.

Drugs against AD are also searched among compounds that increase the general resistance of neurons to noxious factors. One of the investigated group are antiapoptotic compounds – specific inhibitors of signaling cascades activated after cellu-

lar damage and leading to cell death, such as inhibitors of c-jun terminal kinase, e.g. CEP-1347. Another approach are attempts to use neurotrophins, particularly nerve growth factor. Recently, an attempt was undertaken to treat AD by intracerebral injections of genetically modified cells producing NGF. The success of this approach may be questionable, as in the forebrain of AD patients the receptors for neurotrophins disappear.

Summing up, as for now there are no available drugs that can revert the course of AD. We can and should, however, decelerate the progress of AD by using cholinesterase inhibitors, possibly starting the treatment early, and continuing it with inhibitors of butyrylcholinesterase (which is abundant in the AD brain) even in late stages of the disease. We should also try the preventive measures, of which

the most effective is the reduction of caloric intake. The early introduction of antioxidants, antiinflammatory and anticholesterol agents is also strongly advisable as it may delay considerably the onset of dementia. The therapy starting at the period of evident symptoms of dementia may be not effective, as at that time 50–70% of cholinergic neurons had already been lost.

It is important to remember that intellectual activity is a negative risk factor in AD, and the biological background of this phenomenon may be the increased release of acetylcholine, which stimulates, among others, muscarinic M1 receptors that activate PKC. PKC is a strong activator of α -secretase, and as this enzyme competes with β -secretase. Hence, the intellectual activity may contribute to inhibition of A β formation.

NEW ASPECTS OF THE MECHANISMS OF ANTIDEPRESSANT DRUG ACTION

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Compounds that increase the synaptic availability of biogenic amines have been used as antidepressants for the last forty years. During the past decade, new therapeutic targets have emerged from several arenas.

A large body of clinical and basic research is consistent with the notion that alterations of the hypothalamic-pituitary-adrenocortical (HPA) system are causally related to depression and anxiety. These endocrine abnormalities include: increased activity of HPA axis, elevated concentration of ACTH and cortisol and several defects of glucocorticoid receptors (GR), leading to "glucocorticoid resistance".

It was shown that chronic treatment with antidepressants (imipramine, amitriptyline, reboxetine) increased the number and mRNA expression of GR and decreased the plasma level of cortisol and ACTH. Moreover, antiglucocorticoids such as metyrapone, RU 486, aminoglutethimide, ketoconazole or igmesine have been reported to be efficacious as antidepressants.

Recently, antidepressant-like properties of antagonists of the glutamatergic/NMDA receptors have been demonstrated. It has also been shown that zinc is an inhibitor of the NMDA receptor activity and, like other NMDA receptor antagonists, exhibits antidepressant-like effects in rodent screening tests.

The depression states in humans are very often precipitated by stressful situations. On the other hand, stressors induce multiple changes in the nervous system including alterations in neural structure, similar to the effect of chronic treatment with glucocorticosteroids. Tianeptine, antidepressant facilitating 5-HT uptake and decreasing the extracellular level of 5-HT, attenuates stress-induced morphological changes in the hippocampus (CA₃ apical dendritic atrophy) induced by chronic stress or prolonged corticosterone injection in rats.

This and other findings may suggest a possible neuroprotective effect of antidepressant drugs.