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Review Article

POTENTIAL APPLICATIONS OF DOPAMINE D1 AGONIST AND D2 ANTAGONIST LEK-8829

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Summary: Ergoline derivative 9,10-Didehydro-N-methyl-(2-propynyl)-6-methyl-8-aminomethylergoline bimaleinate (LEK-8829), possesses dopamine (DA) D1 agonistic and D2 antagonistic properties in the nigrostriatal and mesocorticolimbic DAergic pathways. These unique dual effects have suggested that LEK-8829 could effectively restore previously imbalanced functional linkage between D1 and D2 receptors under schizophrenic conditions in which, LEK-8829 could improve both the negative and positive symptoms of schizophrenia. As dopamine D1 receptor agonist, LEK-8829 may also be beneficial in relieving the motor symptoms of parkinsonism, alone, or when co-administered with antiparkinsonic dopamine D2 agonists, such as ergoline derivative bromocriptine. Moreover, antiparkinsonic potential of LEK-8829 may be particularly useful when the treatment of parkinsonism with D2 agonist drugs is complicated by psychosis. Antiparkinsonic properties of LEK-8829 also suggest a lower propensity of the drug for the induction of extrapyramidal syndrome in the treatment of schizophrenia. Furthermore, by blocking dopamine D2 receptors, LEK-8829 could block the incentive for drug-seeking and drug-craving while by stimulating dopamine D1 receptors it could mediate drug reward and gratification. This implies that LEK-8829 could also attenuate the relapse of psychostimulant drug-addiction, while not being addictive by itself.
We conclude that agents with LEK-8829-like dual actions toward dopamine receptors, may represent a new and potent drug class for the treatment parkinsonism, schizophrenia and drug-addiction.

Key words: LEK-8829; D1 agonist; D2 antagonist; antipsychotic; antiparkinsonic; antiaddictive

Introduction

The ergoline derivative, LEK-8829 (9,10-didehydro-N-methyl-(2-propynyl)-6-methyl-8-aminomethylergoline), has been developed as a potential atypical antipsychotic drug with antagonistic actions at dopamine D2 and serotonin 5-HT2 and 5-HT1A receptors (1) in order to be more effective and/or produce fewer side effects than typical antypsichotics (neuroleptic) drugs, such as haloperidol. Although the blockade of dopamine D2 receptors is a prerequisite characteristic of clinically effective antipsychotic drugs, the blockade of dopamine D2 receptors within the basal ganglia often provokes unwanted extrpyramidal syndrome (EPS), characterized by parkinsonism, akathisia, catalepsy, and, after long-term treatment, tardive diskinesia (2). Fortunately, atypical antipsychotic drugs, such as clozapine, were developed that have a lower tendency for the induction of EPS. Clozapine is characterized by higher affinity ratio between serotonin 5-HT2 and dopamine D2 receptors (3). Low propensity for the induction of EPS is thought to depend on the ability of atypical antipsychotics to preferentialy inhibit mesolimbic dopaminergic (DA) system as opposed to neuroleptic drugs that effectively inhibit both mesolimbic and mesostriatal DA systems (4). However, the clinical usefulness of clozapine is hampered with the relatively high risk (1-2% of patients) of agranulocytosis or granulocytopenia (5). In addition to EPS, many currently used antipsychotics, including clozapine, exert other unwanted side effects, such as excessive sedation and signs of autonomic blockade with hypotension (6). Contrary to initial hope, atypical antipsychotics that have been developed so far are not very effective in the treatment of negative symptoms of schizophrenia.

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Ergoline derivatives may affect the central nervous system by an interaction with membrane receptors, including dopaminergic, adrenergic and serotonergic receptors. They can act either as agonists, partial agonists or antagonists at these receptors (7). Initially, the effects of ergoline LEK-8829 were compared to the effects of haloperidol and clozapine on various behavioral tests and in *in vitro* receptor binding studies. All compounds inhibited apomorphine-induced locomotor activity in rats, apomorphine-induced climbing behavior in mice and 5-hydroxytryptophan-induced head twitches in mice and induced catalepsy in rats and in mice. LEK-8829 and clozapine, but not haloperidol, showed a certain degree of mesolimbic selectivity, *i.e.*, they caused more potent inhibition of apomorphine-induced locomotion compared with the induction of catalepsy in rats. In the case of LEK-8829, nonspecific effects that presumably predict a side effect profile, such as potentiation of pentobarbital-induced anesthesia in mice (sedation), antagonism of oxotremorine-induced tremors in mice (anticholinergic activity), spontaneous locomotor activity in mice and norepinephrine-induced lethality in rats (sedation and hypotension), were relatively weak. The results of direct measurements of the influences of LEK-8829 on blood pressure showed that LEK-8829 was relatively weak hypotensive. It has been thus suggested that LEK-8829 might be an efficient antipsychotic with a reduced propensity to cause sedative, anticholinergic and hypotensive side effects. A certain degree of mesolimbic selectivity also pointed toward the possibility of a reduced propensity to cause EPS (8).

LEK-8829 has been shown to possess pure competitive antagonist activities at both 5-HT2 receptors and atpha-1 adrenoceptors in rabbit isolated aorta (7). *In vitro* radioligand binding studies revealed that LEK-8829 possess low affinity for rat striatal 3H-SCH23390-labeled dopamine D1 binding sites and high affinity for striatal 3H-spiperone-labeled D2 and cortical 3H-ketanserin labeled serotonin-2 (5-HT2) sites. The ratio of pKi values 5-HT1/D2 was 1.11 (closer to that of clozapine than haloperidol). Based on these experiments it has been concluded that LEK-8829 may be considered to have atypical antipsychotic potential (8).

Thereafter, the most important findings from behavioral, gene-expression and pharmacological studies in unilateral animal models of striatal dysfunction and cocaine self-administration have revealed that LEK-8829 is a dopamine D1 receptor agonist and D2 receptor antagonist drug.

D1 receptor agonist and D2 receptor antagonist properties of LEK-8829

Gene expression studies have shown that LEK-8829 is an up-regulator of the expression early response genes, such as c-*fos* and ANIA-4, and of the expression of genes for several neuropeptides expressed within the basal ganglia (preprotachykinin, neurotensin, and for opioides (preproenkephalin, dynorphin). In all experiments the regulation of the expression of neuropeptides by LEK-8829 was consistent with the effects of combined treatment with selective dopamine D2 receptor antagonists and D1 receptor agonists (9, 10). Interestingly, the above mentioned effects of LEK-8829 on gene expression within the basal ganglia were also consistent with the increased activity of adenylate cyclase within these subcortical nuclei. It is known, that within the striatum, both D2 antagonists and D1 agonists stimulate the activity of this enzyme.

However, this review focuses only on the findings from behavioral and pharmacological studies, and on speculation about the possible therapeutic roles of LEK-8829 in the treatment parkinsonism, schizophrenia, and the relapse of drug-addiction.

Potential antiparkinsonic effects on hypersensitive striatal dopamine receptors

Rats with unilateral dopaminergic denervation of the striatum, induced by the lesion of the median forebrain bundle with 6-hydroxydopamine (6-OHDA), are often used for *in vivo* screening of potential dopamine agonists or antagonists. The 6-OHDA model can be utilized for the evaluation of directly acting DA agonists, since these drugs induce contralateral (toward the intact side) turning behaviour (11). Furthermore, stimulation by partial 5-HTIA agonists can also induce contralateral turning (12).

On the DA lesioned side, denervational dopaminergic hypersensitivity develops. Upon stimulation with directly acting DA agonists, this results in dopaminergic striatal disbalance, since the stimulation of "hypersensitive" striatal dopamine receptors on the denervated side is more intensive compared to the stimulation of "normosensitive" striatal dopamine receptors on the intact side. In contrast, indirectly acting dopamine agonists, such as amphetamine, induce dopaminergic disbalance that results in ipsilateral turning (toward the lesioned

side), since these drugs could release dopamine only within striatum of the intact side. Since LEK-8829 was known to possess D2 antagonistic activity, we expected that LEK-8829 might inhibit the ipsilateral turning induced by amphetamine. Surprisingly, pretreatment with LEK-8829 *per se* induced long-lasting, dose-dependent contralateral turning behaviour, hinting its agonistic avctivity at dopamine receptors.

The receptor mechanism induced by LEK-8829 was then analyzed pharmacologically by the pretreatment of 6-OHDA-lesioned animals with antagonists of dopamine D1, D2 and 5HT1-A receptors, SCH23390, haloperidol and pindolol, respectively. It was found that only the specific D1 receptor antagonist SCH-23390 but not the D2 receptor antagonist haloperidol or 5-HT1A antagonist pindolol, dose-dependently inhibited the turning behaviour induced by LEK-8829. We concluded, therefore, that at least within DA hypersensitive striatum, LEK-8829 is having intrinsic activity at dopamine D1 receptors (9).

We also investigated the proposed D2 antagonistic activity of LEK-8829 at hypersensitive dopamine D2 receptors, by exploring the interaction of LEK-8829 with the dopamine D2 receptor agonist bromocriptine (2-bromo-alpha-ergokryptine). Treatment with either LEK-8829 or bromocriptine induced a vigorous contralateral turning response. Contralateral turning induced by the combined treatment was of similar intensity as the turning induced by single-drug treatments. These results may be explained by the known adaptations to long-term striatal dopamine depletion that result in the development of so called functional »uncoupling« of supersensitive dopamine receptors, where the locomotor stimulation induced by selective agonist of one type of dopamine receptors (e.g. D1) may not be blocked by the blockade of the other type of dopamine receptors (e.g. D2), in contrast to the inhibition of turning that occurs in models with intact, "functionally coupled" dopamine receptors. Accordingly, in our experiment, the pretreatment with selective D1 antagonist SCH-23390 did not have a significant effect on bromocriptine-induced turning, but significantly decreased the turning observed after the combined LEK-8829/bromocriptine treatment (13). We also found that LEK-8829 inhibited contralateral turning induced by D2 agonist quinpirole, but again, only if the rats were co-treated with SCH-23390 (10). We reasoned, that in the 6-OHDA model, the contralateral turning mediated by tLEK-8829, occurs due to intrinsic activity of LEK-8829 on dopamine D1 receptors, while the contralateral turning induced by bromocriptine may be inhibited by concomitant D2 antagonistic activity of LEK-8829. As D1 agonist, LEK-8829 thus by itself has an antiparkinsonic potential that may be particularly useful in situations when the treatment of parkinsonism with D2 agonists, such as with bromocriptine, is complicated by psychosis provoked by over-stimulation of dopamine D2 receptors.

Potential antypschotic effects on normosensitive striatal dopamine receptors

In contrast to parkinsonism, denervational dopaminergic hypersensitivity does not seem to be the underlying mechanism of derranged dopaminergic activity in schizophrenia. Instead, the dopaminergic concept of schizophrenia pathogenesis is based on regional imbalance of brain DA function that arises from dysfunction of D1 receptors in the medial prefrontal cortex (mPFC) and hyperactivity of D2 receptors in ventral tegmental area (VTA) and nucleus accumbens (NAc) (14). The hypothesis of the above regional receptor disbalance in schizophrenia has resulted in the prediction that LEK-8829 may serve also as a potential candidate for the treatment of the negative symptoms schizophrenia.

Rats with unilateral striatal lesions with ibotenic acid (IA) may be used for analysis of pharmacological effects of the drug on presumably normosensitive striatal dopamine receptors. In contrast to unilateral model of parkinsonism, in IA model the rats circle ipsilaterally (toward the lesioned side) when challenged either with directly or indirectly acting DA agonists. Unexpectedly, LEK-8829 induced a dose-dependent contralateral turning also in IA model. Like in 6-OHDA model, LEK-8829-induced contralateral turning was blocked by D1 receptor antagonist SCH-23390. We assumed that contralateral turning in unilateral IA model may be a consequence of simultaneous blockade of dopamine D2 and stimulation of dopamine D1 receptors. Accordingly, we found that the combined treatment with D1 receptor agonist SKF-82958 and D2 antagonist haloperidol also resulted in contralateral turning of IA rats. In control rats, the treatment with SKF-82958 induced ipsilateral turning, whereas the treatment with haloperidol induced contralateral posture. When the rats were treated first with LEK-8829 followed with bromocriptine, the rats changed the direction of turning from contralateral to the ipsilateral side. This result was interpreted as the

consequence of the competition of bromocriptine with LEK-8829 at normosensitive dopamine D2 receptors. We reasoned that depending on the concentration ratio bromocriptine/LEK-8829 at dopamine receptors, bromocriptine could displace LEK-8829 from dopamine D2 receptors (and vice versa). If stimulatory activity of bromocriptine prevails, this results in ipsilateral turning due to co-stimulation of dopamine D2 and dopamine D1 receptors, by bromocriptine and LEK-8829, respectively (15).

Microinjection experiments with LEK-8829 in mPFC, VTA and NAc shall be performed in the future, to determine its D1 stimulation/D2 inhibition effects within the brain regions known to be involved in positive and negative symptoms of schizophrenia.

Potential antiaddictive effects on dopamine receptors within the reward system

In clinical studies, dopamine D1 agonists and D2 antagonists have been used with limited success for cocaine addiction treatment. The main disadvantage of selective D1 agonists as potential treatment medications is their reinforcing and thus abuse potential and selective D2 antagonists have an unfavorable profile of side-effects, since they commonly induce severe EPS.

Self-administration studies show that selective dopamine D1 or D2 receptor agonists have reinforcing properties and can mimic the discriminative stimulus produced by cocaine and stimulate locomotor activity. In contrast to their synergistic responses in most physiological and behavioral actions, dopamine D1 and D2 receptors seem to have opposing effects on relapse to cocaine-seeking behaviour (16). Some studies have shown that while systemic injection of selective D2 agonists potentiates the ability of cocaine to induce cocaine-seeking and that D2 agonists themselves induce cocaine-seeking behaviour, selective D1 agonists attenuate the ability of cocaine to induce cocaine-seeking behaviour and suppress the initiation of cocaine self-administration. These findings suggest that D2-like dopamine receptors could mediate the incentive for drug seeking and promote drug craving while D1-like dopamine receptors could mediate drug reward and gratification (17). In this regard it is noteworthy that drug reward and gratification may be conveyed by synergistic stimulation of the expression of endogenous opioides within the reward system by the above mentioned dual pharmacological profile of LEK-8829 at dopamine D1 and D2 receptors.

The extinction and reinstatement paradigm of animal drug self-administration is considered as a model of human drug-craving and relapse. We have used the model of *i.v.* self-administration of cocaine by rats to test the effects of LEK-8829 on reinstatement of extinguished cocaine-seeking and on cocaine self-administration. We speculated that by concomitant stimulation of D1 receptors and inhibition of D2 receptors, LEK-8829 might attenuate reinstatement of cocaine-seeking induced by cocaine injection and serve at the same time as maintenance and as antagonist drug. In view of its D1 agonistic effects, LEK-8829 was also tested for its reinforcing properties. We have found that the pretreatment with systemic injections of LEK-8829 attenuated reinstatement of cocaine seeking induced by cocaine priming injections and diminished cocaine intake in cocaine self-administration sessions. LEK-8829 itself did not induce reinstatement of cocaine- seeking and did not maintain intravenous self-administration (18). These findings indicate that LEK-8829 is a candidate medication for the treatment of cocaine craving in cocaine addiction. As mentioned above, LEK-8829 was also found to increase the synthesis and release of endogenous striatal opioid peptides, an action that may contribute to its anti-addictive potential.

Conclusion Remark

Although many questions regarding the beneficial mechanisms of LEK-8829 in parkinsonism, schizophrenia and drug-addiction remain to be addressed, it appears that agents with dual actions toward DA receptors may represent a new and potent drug class for the treatment of these disorders. LEK-8829 may be particularly useful whenever the treatment of parkinsonism with D2 agonist drugs, is complicated by psychosis. Antiparkinsonic properties of LEK-8829 also suggest a lower propensity of this drug for the induction of EPS in the treatment of positive symptoms of schizophrenia. Furthermore, by blocking dopamine D2 receptors, LEK-8829 could block the incentive for drug-seeking and drug-craving while by stimulating dopamine D1 receptors it could mediate drug reward and gratification. This implies that LEK-8829 could also attenuate the relapse of psychostimulant drug-addiction, while not being addictive by itself.

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POTENTCIALNA UPORABNOST LEK-8829, AGONISTA DOPAMINSKIH RECEPTORJEV D1, IN ANTAGONISTA DOPAMINSKIH RECEPTORJEV D2

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Povzetek: Ergolinski derivat 9,10-didehydro-N-methyl-(2-propynyl)-6-methyl-8-aminomethylergoline bimaleinate (LEK-8829) je agonist dopaminskih receptorjev D1 in antagonist dopaminskih receptorjev D2 v nigrostriatnem in mezolimbično-kortikalnem dopaminergičnem sistemu. Ta edinstveni dvojni receptorski učinek LEK-8829 nakazuje možnost poprave posledic funkcionalnega razklopa dopaminskih receptorjev D1 in D2 pri bolnikih s shizofrenijo, pri čemer bi zato LEK-8829 lahko ublažil tako pozitivne kot negativne simptome te duševne bolezni. Samostojno ali skupaj z ergolinskim derivatom bromokriptinom, antiparkinsonikom z agonističnim delovanjem na dopaminskih receptorjih D2 bi LEK-8829 s spodbujanjem dopaminskih receptorjev D1 lahko ublažil motorične simptome parkinsonizma, z zaviranjem dopaminskih receptorjev D2 pa bi hkrati zmanjševal nevarnost za nastanek psihoze, ki je možen zaplet zdravljenja parkinsonizma z agonisti dopaminskih receptorjev D2. Antiparkinsonski učinki LEK-8829 obetajo tudi manjšo nagnjenost LEK-8829 za povzročanje ekstrapiramidnega sindroma pri zdravljenju shizofrenije z LEK-8829. Še več, z zaviranjem dopaminskih receptorjev D2, bi LEK-8829 pri osebah zasvojenih s psihomotoričnimi stimulansi, morda zmanjšal intenzivnost apetitivnega vedenja (hlepenja) povezanega z iskanjem droge, s spodbujanjem dopaminskih receptorjev D1 pa bi, s posnemanjem nagrajevalnih in hedonističnih učinkov droge, ublažil posledice umanjkanja teh učinkov med abstinenco. Tako bi LEK-8829 lahko preprečeval recidiv zasvojenosti, pri čemer pa sam ne bi imel zasvojevalnega učinka.
Sklepamo, da bi snovi z dvojnim učinkom na dopaminskih receptorjih, tako kot LEK-8829, lahko predstavljale novo vrsto učinkovitih zdravil za zdravljenje parkinsonizma, shizofrenije in zasvojenosti z drogami.

Ključne besede: LEK-8829; D1 agonist; D2 antagonist; antipsihotik; antiparkinsonik; antiaditiv