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Altered central vision and amacrine cells dysfunction as marker of hypodopaminergic activity in treated patients with schizophrenia

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Abstract

Background

Retinal dysfunction is widely documented in schizophrenia using flash (fERG) and pattern electroretinograms (PERG), but the role of dopamine transmission has seldom been explored.

Methods

We explored the role of dopamine transmission by evaluating the spatial location of retinal anomalies using multifocal ERG (mfERG) in photopic condition and the oscillatory potentials (OPs) extracted from fERG measured in scotopic condition in 29 patients with schizophrenia and 29 healthy controls.

Results

With the mfERG, our main results revealed reduced amplitudes in the center of the retina: P1 ($p < .005$) and N2 amplitudes ($p < .01$) in the <2° region, N1 ($p < .0005$) and P1 amplitudes ($p < .001$) in the 2–5° region and P1 amplitude ($p < .05$) in the 5–10° region. For

considered as a measure to evaluate the hypodopaminergy in patients.

Introduction

The retina is an easily accessible part of the central nervous system and an appropriate site to investigate neurotransmission abnormalities in schizophrenia (Lavoie et al., 2014), especially dopaminergic transmission. Studies conducted in the past decade have focused on structural and functional abnormalities of the retina (Adams and Nasrallah, 2018; Silverstein and Rosen, 2015), and retinal functional abnormalities are now firmly established. Flash electroretinogram (fERG) measurements have shown that several stages of retinal processing are disrupted in schizophrenia. The amplitude of electrical signals is reduced in the rod and cone photoreceptors and bipolar cells, in both scotopic and photopic conditions, irrespective of the antipsychotic dose (Balogh et al., 2008; Bernardin et al., 2020; Hebert et al., 2015; Warner et al., 1999). Transmission in the retinal ganglion cells (RGC) is also altered in schizophrenia (Demmin et al., 2018; Moghimi et al., 2020). Using the pattern electroretinogram (PERG), we recently reported a delay in the emission of action potentials by the RGC as evidenced by an increase in N95 implicit time (Bernardin et al., 2020). Retinal function could thus provide potential biological markers for clinical practice. For instance, when comparing patients with bipolar disorders and schizophrenia, fERG anomalies could distinguish patients with schizophrenia from healthy controls with 0.91 accuracy, 77% sensitivity and 91% specificity (Hebert et al., 2020).

In this context, we focus on the role of dopaminergic transmission in signal processing in the retina, which is required to understand both the potential impact of antipsychotic drugs and the hyperdopaminergy during the acute phase. Although several functional abnormalities of the retina have been shown to be independent of antipsychotics, which signals are related to dopaminergic transmission remains to be established. Knowing that dopaminergic dysfunctions are a keystone of the pathophysiology of schizophrenia (Howes et al., 2015), it is important to emphasize that dopamine is involved in fERG responses (Demmin et al., 2020; Desai et al., 1997; Nasser et al., 2013; Roy et al., 1997). Oscillatory potentials (OPs) appear to be a good candidate among fERG measures when looking for a dopamine neurotransmission-related measure, as shown in many studies in animal models and humans (Gutiérrez and Spiguel, 1973; Harnois et al., 1987; Jaffe et al., 1987; Marmor et al., 1988; Wachtmeister and Dowling, 1978). OPs reflect rod and cone interactions (Wachtmeister, 1973a; Wachtmeister, 1973b; Wachtmeister, 1987) and thus photoreceptors and bipolar cells activity (Wachtmeister, 1998). Other studies have suggested that they can be dependent of retinal mic

are dopaminergic (Kolb et al., 1981; Ortuño-Lizarán et al., 2020) and dopamine has been suggested to be involved in the generation of OPs (Wachtmeister, 1998). OPs are small rhythmic wavelets superimposed on the ascending b-wave of the ERG and are thought to reflect the activity initiated by amacrine cells in the inner retina (Wachtmeister, 1998), among which several subtypes are dopaminergic (Kolb et al., 1981). OPs are composed of three major peaks (O1, O2 and O3) and a smaller fourth peak (O4) that is less reproducible and is not considered as reliable data. The first three originate from the inner plexiform layer (Ogden, 1973), and are altered by dopamine blockers such as haloperidol or chlorpromazine (Bartel et al., 1990; Holopigian et al., 1994; Wachtmeister, 1981). Only few studies have explored OPs in schizophrenia. The first study showed greater amplitude variance in male patients (Raese et al., 1982) but this result was not replicated (Schechter et al., 1987). Another study with a small sample comparing 12 unmedicated patients with schizophrenia and nine healthy controls investigated OPs response but failed to show any difference between the groups (Marmor et al., 1988). The most recent study showed only slight differences between patients with schizophrenia and healthy controls that depended on the gender (Moghimi et al., 2020). These authors analyzed OPs based on the frequency band split (75–100 Hz low-frequency OPs, 100–300 Hz high-frequency OPs, and a combination of the first two, between 75 and 300 Hz) and no effect was shown. These studies require replication: none measured OPs according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards and the potential link with the dopaminergic effect of antipsychotic medication was not explored.

To further assess the link between dopamine and the retina transmission impairments, we analyzed the spatial distribution of these anomalies. As a matter of fact, fERG and PERG measurements only provide information about the overall response of the retina (Bach et al., 2013), whereas dopamine receptors are especially present in the fovea (Savy et al., 1991). In patients with Parkinson's disease, the amplitude of the P1 wave was found to be reduced in the fovea (<2°) (Moschos et al., 2011). These results confirm the implication of dopamine in the reduced response of the multifocal ERG (mfERG), and to an even greater extent, in the center of the retina (Bodis-Wollner, 2013). If dopamine is involved in the abnormalities of retina transmission in patients with schizophrenia, then these abnormalities should be more marked in the center than at the periphery. mfERG recordings enable the evaluation of multiple local responses, and hence to contrast central and peripheral responses.

Considering the results of the literature, we hypothesize that OPs is a good candidate to explore dopaminergic dysregulation (whether due to medication or dopamine transmission alteration). Our second hypothesis is that dopamine abnormalities would preferentially be found in the central retina where dopamine receptors are more concentrated. The reduced amplitude of the OPs and the central vs. peripheral distribution of the retina t

Study population

This study is part of a larger project, Causa Map, which investigate the effect of regular cannabis use on the visual system (Schwitzer et al., 2017). The study was registered with clinicaltrials.gov (identifier: NCT02864680). The impact of cannabis on the emergence of schizophrenia symptoms justified the inclusion of 29 patients with schizophrenia (median age [95% CI]: 24 [25:31]) and 29 healthy matched controls (24 [23:27]) for age in the study (Table 1). Recruitment details are provided in...

Demographic and clinical characteristics

No significant difference in age was found between the controls and the patients with schizophrenia ($U = 384.5$, p = n.s). Differences in the number of years of education were found between the groups ($U = 95.5$; $p < .001$) (Table 1).

Among the 29 schizophrenia patients, 3 were cannabis users tested positive for THC, and 16 were alcohol users. No difference in CAST scores was found between controls and schizophrenia patients ($U = 364.0$, p = n.s), AUDIT scores were low in both groups, but...

Discussion

Several results point to the involvement of dopaminergic neurotransmission in the abnormal retinal transmission observed in patients with schizophrenia.

First, our result showed reduced amplitudes of the O1, O2, O3 waves and a reduced overall index of O1, O2 and O3 amplitudes in patients with schizophrenia. To our knowledge, this is the first report of reduced amplitudes of the OPs in a sample of medicated patients with schizophrenia. Our results in medicated patients with schizophrenia contrast ...

Conclusion

In conclusion, patients with schizophrenia showed reduced amplitudes of the cones system preferentially in the central zone of the retina, and reduced OPs amplitudes. Both may reveal a hypodopaminergic effect, induced by antipsychotic drugs or related to the pathophysiology. Hence, further studies are indispensable in drug naïve patients with an at-risk mental state

financial relationships that could be construed as a potential conflict of interest....

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CRediT authorship contribution statement

This study met the requirements of the Declaration of Helsinki (World Medical Association, 2013), was approved by the Nancy University Hospital Ethics Committee (2013-A00097-38 CPP 13.02.02) and was registered with clinicaltrials.gov (identifier: NCT02864680).

Before taking part in the study, volunteers signed consent forms detailing all aspects of the research....

References (69)

R. Warner *et al.*
Retinal function as a marker for cell membrane omega-3 fatty acid depletion in schizophrenia: a pilot study
Biol. Psychiatry (1999)

S.M. Silverstein *et al.*
Schizophrenia and the eye
Schizophr. Res. Cogn. (2015)

T. Schwitzer *et al.*
Spatial localization of retinal anomalies in regular cannabis users: the relevance of the multifocal electroretinogram
Schizophr. Res. (2020)

T. Schwitzer *et al.*
Delayed bipolar and ganglion cells neuroretinal processing in regular cannabis users: the retina as a relevant site to investigate brain synaptic transmission dysfunctions
J. Psychiatr. Res. (2018)

A.D. Rubinsky *et al.*
Estimating risk of alcohol dependence using alcohol screening scores
Drug Alcohol Depend. (2010)

P. Moghimi *et al.*
Electoretinographic evidence of retinal ganglion cell-dependent function in schizophrenia
Schizophr. Res. (2020)

M.H. Meier *et al.*
Retinal microvessels reflect familial vulnerability to psychotic symptoms: a comparison of twins discordant for psychotic symptoms and controls
Schizophr. Res. (2015)

P. Mailankody *et al.*
The role of Optical Coherence Tomography in Parkinsonism: a critical review
J. Neurol. Sci. (2019)