Principles and Practice of Clinical Electrophysiology of Vision

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Neuropsychiatric Drug Effects on the Visual Nervous System

Walter G. Sannita

COMPOUNDS USED IN THE TREATMENT OF PSYCHIATRIC CONDITIONS

Neuroleptics, antidepressants, and central nervous system (CNS) excitants act on the CNS aminergic subsystems through synaptic blocking, inhibitors of reuptake, and potentiation of transmitter release or direct postsynaptic action, respectively. The affinity with different receptor-neurotransmitter systems can vary and is neither totally selective nor necessarily consistent across species. Different compounds can therefore yield different effects[66, 74] (Table 22–1). Lateralized effects on the visual evoked potential (VEP) have been also described (Table 22–2).[80]

In in vitro retina models, fluphenazine increases the electroretinographic (ERG) rod b-wave over a wide range of drug concentrations without detectable effects on the PIII component[72]; a reduction of the ERG b-wave was conversely observed after haloperidol administration.[71] Chlorpromazine, 1 to 10 mg intravenously (IV), decreases the ERG b- and c-wave in sheep,[9] while 3 to 8 and 12 mg/kg increase the ERG amplitude in rabbits and rats, respectively.[42, 79] An increment in VEP latency (often associated with reduced amplitude) is evident in animals, hyperkinetic children, and psychotic patients after the administration of most neuroleptics.[37, 57, 62, 66, 74] The long-term administration of high doses of thioridazine is known to induce a retinopathy due to local toxicity on the pigment epithelium and is associated with flash ERG suppression and reduced electro-oculographic (EOG) reactivity (see Chapter 78). A selective suppression of the O_2 components of the oscillatory potentials (OPs) was reported in rats[11] (Table 22–3). Regardless of local damage, increased a-wave latency and prolonged evolution and reduced amplitude of b-waves after acute administration of doses as low as 50 mg have been documented in healthy volunteers.[22]

Amphetamines and related compounds usually decrease VEP latencies and increase the amplitude.[66, 74] These effects, however, are not constant, mostly due to patient variability as to the baseline condition and clinical and/or electrophysiological response to drug action. In general, VEP measurements seem to be more sensitive in these studies to the level of vigilance than to drug action.[32] Methamphetamine reduces the ERG b-wave in isolated retina.[52]

With the exception of accommodation, ocular side effects are unusual during treatment with antidepressive drugs. A dose-related increase in the ERG b-wave amplitude was reported after amitriptyline in isolated retina[52] as well as after the oral administration of nomifensine to healthy volunteers.[24] Lithium (an antimanic compound thought to enhance serotoninergic function and intracellular calcium) did not alter the flash VEP of patients receiving long-term treatment[36, 76] or the flash ERG and pattern VEP[82] of volunteers after the administration of

TABLE 22–1.
Classification of Some Established (Neuroactive) Compounds by ERG Effect

Reduced ERG b-Wave Amplitude			
Without Latency Changes	Associated Latency Increase	Associated a-Wave Changes	Associated c-Wave Changes
Haloperidol	Thioridazine	Thioridazine	Chlorpromazine*
Chlorpromazine*			
Methamphetamine			
Diphenylhydantoin†			
Anesthetics*			
Urethane			
Halothane			

Increased ERG b-Wave Amplitude		
Without Latency Changes	Associated Latency Decrease	Associated Latency Increase
Fluphenazine	L-Dopa	Alcohol
Chlorpromazine*		
Amytriptyline		
Diphenylhydantoin*		
Anesthetics*		
Nomifensine		
Barbiturates*		
Atropine		
Steroids		

Reduced ERG a-Wave Amplitude
Associated b-Wave Changes
Diazepam

*Contrasting effects depend on the experimental condition or are dose related.
†Unsystematic effects.

TABLE 22–2.
Classification of Some Established (Neuroactive) Compounds by Effect on VEPs

Increased VEP Amplitude		
	Associated Latency	
Without Latency Changes	Increase	Decrease
Lithium*	Triiodothyronine	Amphetamine
Amphetamine		
Barbiturates†		
L-Acetylcarnitine		
Tobacco smoking*		
Tobacco withdrawal*		
LSD†		

Decreased VEP Amplitude	
Without Latency Changes	Associated Latency Increase
Diazepam	Neuroleptics
Sodium valproate	Barbiturates†
Neuroleptics*	Marijuana*
Gaseous anesthetics	
LSD†	
Marijuana†	
Alcohol*	
Tobacco smoking*	
Tobacco withdrawal*	

*Unsystematic effect.
†Contrasting effects depend on the experimental condition or are dose related.

doses yielding clinically relevant drug serum levels. An increase in pattern VEP amplitude up to values higher than those in healthy controls was conversely observed in patients after 1 to 5 weeks of treatment; there were no systematic changes in latency.[20]

L-DOPA

L-Dopa, a precursor of dopamine, is used as a substitute (dopamine itself does not cross the blood-brain barrier) in Parkinson's disease and related syndromes. The VEP latency (especially to transient or steady-state pattern stimulation) is increased in patients with Parkinson's disease[3, 4] and in experimental animals treated with inhibitors of monoamine synthesis or blockers of dopamine receptors.[4, 57] In animal models of Parkinson's disease, the ERG b-wave is increased in latency and decreased in amplitude, and the OP's amplitude is reduced.[87] The evidence of abnormal retinal function in patients derives from EOG studies as well.[18] The VEP abnormalities that depend on the stimulus characteristics (especially spatial frequency), are worsened by neuroleptic drugs such as chlorpromazine and haloperidol, and revert after the administration of dopamine agonists (e.g., apomorphine) or L-dopa.[3, 4, 16, 28, 43, 62] After acute L-dopa administration to healthy volunteers, no effect was detected on the flash VEP,[88] but increased amplitude and decreased implicit time of the ERG b-wave were reported.[25]

TABLE 22–3.
Classification of Some Established (Neuroactive) Compounds by Effect on Retinal Oscillatory Potentials

Decreased Amplitude	Increased Amplitude (Associated Latency Decrease)	Reduced Latency
Thioridazine	Barbiturates*	L-Acetylcarnitine

*Opposite effect at high doses.

MINOR TRANQUILIZERS

Diazepam and related compounds (e.g., oxazepam, chlordiazepoxide, nitrazepam, flurazepam) reduce the amplitude of the flash VEP in animals,[75] normal humans,[14, 17, 59] and photosensitive epileptic patients,[8, 17] as well as the pattern VEP in normal volunteers.[5] Drug effects on either early or late components or involving the whole VEP waveform were reported to depend on the experimental conditions and the administered compound[46, 74]; a hangover effect was described for some compounds.[46] Changes in latency are reportedly less systematic. Barbiturates (e.g., phenobarbital) at low doses share the anxiolitic action of benzodiazepines, but not the effects on VEP; increased latency was described and eventually associated with reduced amplitude.[15, 74]

ANTIEPILEPTIC DRUGS

Diphenylhydantoin increases the ERG b-wave in in vivo animal models.[10] In in vitro preparations the amplitude is increased or decreased depending upon dose,[40] and there is a K-related protective effect against hypoxia.[41] Pattern VEP at very low contrast was the only evoked phenomena to be found abnormal in a patient with diphenylhydantoin intoxication.[48] Sodium valproate (a compound thought to act by increasing the γ-aminobutyric acid [GABA] brain concentration) proved ineffective on the pattern VEP of healthy volunteers up to 1,000-mg acute doses,[33] while comparable doses reduced the flash VEP amplitude in photosensitive epileptic patients.[38] This latter effect is attributable to the abnormally large flash VEPs that are common in these patients,[7] and are normalized by sodium valproate[19] and diazepam.[17] In these patients, the flash ERG is comparable to that of normal individuals except for significantly shorter implicit time[7]; a reduction in a-wave amplitude and latency[8] and an increased duration of the b-wave (without significant amplitude changes)[17] were reported after diazepam administration. Ocular side effects of carbamazepine are unusual and mostly depend on the compound's mild effect on accommodation; lesions of the retinal pigment epithelium[55] and impaired contrast sensitivity[81] have been reported, however.

ANESTHETICS

In humans, inhaled anesthetics reduce the VEP amplitude, this effect involving early or late components or the whole VEP waveform, depending upon the compound administered. A concentration-related reduction in pattern VEP amplitude without any latency change was described after nitrous oxide administration to healthy volunteers.[21] Low doses of barbiturates increase human VEPs, which are then suppressed at doses inducing deep levels of anesthesia.[74] In in vitro and in vivo animal studies ERG and OP amplitudes are increased, and OP implicit time is decreased at low doses of barbiturate; these effects are reversed at higher doses. Anesthetic doses of chlorpromazine, chloral hydrate, diazepam, etc., increase the ERG amplitude.[26] The flash ERG amplitude is decreased in animals by urethane and inhaled anesthetics such as halothane[78]; the halothane effect is counterbalanced by nitrous oxide. Halothane and other anaesthetics slow the course of dark adaptation by decreasing the rate of rhodopsin regeneration.[83]

CHOLINERGIC AND ANTICHOLINERGIC COMPOUNDS

Cholinergic transmission is thought to be involved in the processing of information throughout the visual system,[45] and cholinergic compounds are being proposed as potentially useful in the treatment of dementia.[2] Atropine increases the b-wave amplitude in vitro,[52] but the effects of anticholinergic drugs on visual evoked phenomena are controversial,[1, 68] and cholinergic-sensitive channels within the visual system have been suggested to conceivably account for these discrepancies.[34] Compounds increasing cholinergic synaptic action (e.g., carbamates, organophosphates) dramatically reduce the pattern VEP amplitude to stimuli of low spatial frequency.[45] L-Acetylcarnitine (a putative cholinergic compound) decreases the OP latency in humans[70] and induces in animals an increment in pattern VEP amplitude that is reversed by atropine.[58]

HORMONES

Endocrine alterations involving thyroid, parathyroids, and adrenal cortex, for example, can result in VEP modifications that are reversed by proper treatment; triiodothyronine increases both the VEP amplitude and latency when administered to healthy volunteers, whereas parathyroid extracts are ineffective.[74] Corticosteroids affecting the Na/K balance reportedly increase the ERG b-wave amplitude[86]; the effect of glucorticoids on the retina is, however, controversial and was reported only at extremely high doses.[54, 89] Similarly, no effect on VEP was observed in healthy volunteers.[74]

DRUGS OF ABUSE

Ocular effects have been described for most drugs of voluntary use or abuse[51]; the electrophysiological approaches have been unsystematic, and contrasting findings, probably due to individual variability, have often been described. An increased latency and reduced amplitude of several VEP components were described after tetrahydrocannabinol use,[47] while other authors have observed no systematic effect.[64, 49] Early studies in humans reported a reduction in VEP amplitude after lysergic acid diethylamide (LSD) use[74] that eventually depended on K-mediated reduced neuronal firing[12]; an increase in amplitude was also reported in animals.[77] Psilocybin is apparently inactive on the visual system.[74]

A reduction in VEP amplitude (occurring to a greater extent for later components)[63, 74] and a leveling of hemispheric asymmetries[63, 65] were described in animals and humans after both acute administration and chronic intake of alcohol; the ERG b-wave amplitude is classically reported to be increased by alcohol in animal models, and an increase in latency has been observed in humans.[83]

After tobacco smoking, both a reduction[31, 61] and an increase[27] in VEP amplitude were observed; contrasting findings were also reported during smoking withdrawal,[27, 61, 67, 74] these discrepancies being possibly accounted for by the experimental setting and/or the neuropsychological status. Abstinence from smoking can eventually be relevant in clinical diagnostic routines.[61, 67, 74]

CONCLUSIONS

Visual information is processed in vertebrates through mechanisms of neurotransmission that are shared by retina and brain structures.[30, 39, 50, 53, 60] If the special properties of the (photo) receptors can be disregarded, the retina has little or no relevant input from the CNS and is peculiarly convenient for in vitro pharmacological studies, and a comparison of the evoked phenomena recorded from retinal preparations with those obtained in vivo is an approach to be favored in neuropharmacology.

The information available is, however, still incomplete and does not allow an operational classification of drug effects on the visual system. For many established neuroactive compounds, visual side effects have been documented in humans without any report on electrophysiological changes, although these should have been detectable in the presence of drug-related visual impairment.[29, 51] Many compounds of medical use that exert no primary action on the CNS have been also reported to induce visual side effects detectable electrophysiologically. A list should include cardiac glycosides,[85] antibiotics,[44] ethambutol,[23] ergotamine,[35] etc. β-Agonists active on systemic blood circulation (e.g., theophylline, papaverine, buphenine) are active on the retina in isolated eye preparations,[13, 56, 73] although an effect on humans has not been documented. Compounds of nonmedical use can also be active on the CNS, and ERG or VEP effects have been reported (e.g., insecticides[6, 45]). There is also evidence from human studies that fluctuations within normal limits of blood chemistry such as glucose levels and [NH_4] can change clinical electrophysiological results.[69] In most studies, dose-response relationships were not investigated despite the evidence that different dosages can eventually yield contrasting effects.[40] In addition, few in vivo studies have included a correlative analysis of drug effects on all retinal and cortical evoked phenomena, and interest has been often focused on the (traditionally) most significant ERG or VEP components.

The ERG or VEP changes induced by neuroactive compounds and outlined above are seldom apparent in a single patient's recording and are in most cases identified when the population statistics of control and treated groups are compared. Their relevance can be limited whenever standard electrophysiological procedures are used to test vision in the clinical setting; drug-dependent modifications are, however, an additional source of intraindividual variability and are potentially critical in research protocols not purporting the identification of drug effects as a primary hypothesis to be tested.

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