Effects of centrally depressant drugs on pupillary function: significance for normal and diseased subjects

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1 The response of the pupil to centrally depressant drugs is discussed and the technique to induce cyclical variations in pupil size is described.

Keywords centrally acting drugs pupillary function

There are few structures in the human body that are as beautiful, as sensitive to external factors, and as sharply delineated, as the iris. Because of the delicacy of the nervous control of the iris, it often has been used in both basic and applied medical research, mainly to study the functional state of the neuro-vegetative system (Ishikawa *et al.*, 1977), or that of the anterior visual pathways (Thompson, 1976).

Although a great many studies have been devoted to the effects of centrally depressant drugs on various biological functions, it is surprising how little attention has been paid to the effects of these drugs on pupillary function. Apart from a number of psychological studies, generally using pupillography, for the evaluation of the influence of centrally acting drugs (Kotzan, 1978), little has appeared in the literature. Furthermore, although interesting information was provided in the few studies that were reported, it did not receive as much attention from the clinicians as it deserved.

My purpose is to emphasize the importance of pupillary modifications as a reflection of the effect of centrally depressant drugs, and more specifically that of benzodiazepines. I would like to draw attention to possible consequences of these modifications on the functional state of the normal subject and on the evaluation of the visual system of the diseased patient.

The pupillary light reflex is diminished by diazepam. This has clearly been demonstrated in the cat by means of electrophysiological

recordings of the activity of the short ciliary nerves, that innervate the pupillary sphincter (Sigg & Sigg, 1973).

There are probably many factors involved in this diminished response.

Basically, the light reflex is induced by the visual input to the retina. Now, in the inner plexiform layer of the mammalian retina, high affinity binding sites for diazepam have been found, that show properties similar to those found in the brain (Skolnik *et al.*, 1980) as well as dependence on environmental illumination, which suggests that these benzodiazepine receptors are involved in the physiological mechanisms of vision (Biaggio *et al.*, 1981), and hence in the pupillary light reflex.

Although not located precisely in the reflex arc, there is another place in the primary visual pathways, i.e. the occipital lobe, whose activity has been thought to affect the light reflex (Reuther *et al.*, 1981). Now, in the cerebral cortex too, a very high density of specific binding sites for benzodiazepines has been demonstrated. Thus, the occipital lobe is another structure by which benzodiazepines possibly influence the pupil light reflex.

It has also been shown that the pupillary light reflex is modulated by numerous nervous structures located outside of the visual pathways, such as for example in the brainstem (Wyatt & Musselman, 1981; Breen *et al.*, 1983) or in the cerebellum (Hulthorn *et al.*, 1978). The anatomical location of benzodiazepine binding sites

has not yet been completely described, and there are still insufficient data for extensive anatomico-function correlations. It has been suggested, however, that benzodiazepines might, for example, enhance a GABA-ergic inhibitory influence on noradrenergic locus coeruleus cells and, thereby, release pontine generator neurones for pontogeniculooccipital waves (Ruch-Monachon *et al.*, 1967). It is conceivable that this is one of the numerous pathways by which benzodiazepines act indirectly on the light reflex.

There are a number of problems involved in the evaluation of the light reflex. In common clinical practice, a slight alteration in pupil light reflex is often difficult to detect by direct examination of the eye with a flash light (Safran & Roth, 1982). On the other hand, although infrared pupillography is an excellent way of quantifying the pupillary reflex, it implies the use of sophisticated instruments, generally available only in research laboratories. We have devised a simple clinical method, however, which we have called 'pupil cycle induction test', that makes it possible for every ophthalmologist to evaluate the quality of the light reflex with his own standard equipment (Safran *et al.*, 1981a, b).

The procedure is as follows. Using a slit lamp and its microscope, the physician focuses a horizontal slit beam of light on the bottom part of the iris. The slit is then progressively raised until it overlaps the lower margin of the pupil. This induces a contraction of the pupil, preventing the beam of light from reaching the retina. The pupil then dilates, causing the retina to be exposed to the light again. The light is held in this position to induce oscillations of the pupil. The evaluation consists of assessing the regularity of the light-induced oscillation.

The pupil cycle induction test was standardized on 186 presumably normal eyes. Ninety-four per cent of them exhibited induced pupillary oscillation that lasted for more than two runs of 40 successive cycles (Safran *et al.*, 1981a). When this examination technique was applied to the 60 eyes of 30 unselected subjects with normal visual function, but undergoing a benzodiazepine or barbiturate treatment, in 30% only more than 40 oscillations could be obtained (Safran *et al.*, 1981b). In view of this open study, we recently performed a controlled

experimental study with volunteers receiving 6 mg of bromazepam a day, using a similar method of pupillary evaluation. Although no significant change was noted in their mean pupillary diameter, all subjects showed a significant irregularity in pupillary oscillation (Walser *et al.*, in preparation). Changes in pupillary oscillation only occurred after 4 days of drug ingestion. This delay in the occurrence of functional change has been previously described, for example in EEG with diazepam administration.

Four conclusions can be drawn from these findings.

First, benzodiazepines do affect pupillary kinetics. This indicates that pupillary adaptation to rapid and repetitive changes in light stimulation is not as effective in patients who had been given benzodiazepine treatment as in untreated control subjects. It is conceivable that changes in pupillary kinetics account for part of the alteration of visual function that has been demonstrated with benzodiazepine administration, for example increase in ocular readaptation time, i.e. prolonged interval during which a subject exposed to a bright light flash cannot perceive a given target (Bergman *et al.*, 1979).

Second, investigation of effect of centrally depressant drugs on pupil function requires prolonged administration.

Third, since modification in pupil response due to depressant drugs is sometimes difficult to distinguish from that due to optic nerve disorders (Safran *et al.*, 1981b), a detailed drug-taking history is necessary when investigating anterior visual pathways by means of pupil function. Unfortunately, the possibility of modification in pupillary function due to the ingestion of central depressant drugs is often overlooked in clinical practice. It is highly significant that in the recent detailed studies of pupillary light response in patients with optic nerve disorder, no indication is generally provided as to whether the studied subjects were taking any central depressant drugs.

Finally, the pupil cycle induction test has proved to be a useful semi-quantitative method for the detection of changes in pupillary function resulting from benzodiazepine ingestion, in otherwise healthy subjects.

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