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β-Blockers and CNS Side-Effects

CNS-Related (Side-)Effects of β-Blockers with Special Reference to Mechanisms of Action

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Summary. β-Adrenoreceptor antagonists are liable to produce behavioural side-effects such as drowsiness, fatigue, lethargy, sleep disorders, nightmares, depressive moods, and hallucinations. These undesirable actions indicate that β-blockers affect not only peripheral autonomic activity but also some central nervous mechanisms. In experimental animals β-blockers have been found to reduce spontaneous motor activity, to counteract isolation-, lesion-, stimulation- and amphetamine-induced hyperactivity, and to produce slow-wave and paradoxical sleep disturbances. Furthermore, central effects such as tranquillizing influences are used for the treatment of conditions such as anxiety. Several different mechanisms of action could be responsible for these CNS effects: (1) Centrally mediated specific actions on centrally located β-adrenergic receptors, known to exist downstream from, and at the terminals of, 'vigilance-enhancing' central noradrenergic pathways. (2) Centrally mediated specific actions on centrally located receptors of the non-adrenergic type; an affinity of some β-blockers towards 5-HT-receptors is well documented. (3) Centrally mediated non-specific actions on centrally located neurones, owing to the membrane-stabilizing effects of β-blockers. (4) Peripherally mediated actions whereby β-blockers induce changes in the autonomic activity in the periphery, which are relayed to the CNS to induce changes in activity of a variety of central systems. It can be assumed that with any one of the β-blockers all these mechanisms come into play, yet with varying degrees depending on characteristics of the drugs such as lipophilicity and hydrophilicity, the ratio of antagonist versus (partial) agonist properties, affinity to 'alien' receptor sites, strength of membrane-stabilizing activity, stereospecific affinity, and potency.

Key words: β-blockers, CNS side-effects, sleep disturbances; anxiolytic properties, hallucinogenic properties, hydrophilicity, lipophilicity, sedation, stereospecific potency

Evidence for CNS-Mediated Effects of β-Blockers

There is ample evidence that β-adrenoreceptor antagonists (β-blockers) affect not only peripheral autonomic functions, but also, though to variable degree, motor and, in particular, behavioural functions. In patients treated with β-blockers for a variety of peripheral autonomic afflictions, additional undesirable effects can be produced: drowsiness, fatigue, lethargy, depressive moods, sleep disturbances, nightmares, hallucinations and occasionally delirious states and paranoid psychosis (Greenblatt and Shader 1972; Jefferson 1974; Fraser and Carr 1976; Fleminger 1978; Gershon et al. 1979; Koehler and Guth 1977; Arensberg and Wenger 1979). Additional observations are reported in this volume by Betts and Alford (1985), Cove-Smith and Kirk (1985), and Westerlund (1985). The very nature of most of these side-effects makes it likely that the β-blockers are capable of affecting central nervous mechanisms as well as peripheral autonomic functions. This interpretation is supported by the well-substantiated experience that β-blockers can be used to treat a variety of typically central nervous disorders. β-Blockers have been employed to treat alcoholism (Carlsson 1976; Freedman 1978), drug-abuse and withdrawal symptoms (Grosz 1973; Ladewig et al. 1978), certain forms of tremor (Floru et al. 1974; Ljung 1979), schizophrenia (Atsmon et al. 1971; Steiner et al. 1972; Yorkston et al. 1978) and above all, anxiety (Lader 1974, 1976; Gosling 1977; Noyes 1982) (reviews; Middlemiss et al. 1981; Patel and Turner 1981; Noyes 1982; Kielholz 1978). There is some evi-

dence, though not unchallenged (van Zwieten 1984), that β-blockers exert their antihypertensive influence in part by influencing some central blood pressure-controlling mechanism.

Experimental data from animal studies, both behavioural and neurophysiological, cannot be explained unless one assumes that β-blockers do affect activity in some central neuronal 'systems'. Spontaneous locomotor activity of mice is reduced by intraperitoneal injections of propranolol, alprenolol, or INPEA (1-(4'-nitrophenyl)-2-isopropyl-aminoethanol; Fabian et al. 1972). Propranolol (L,D- as well as D-) exerts a tranquillizing effect in rats conditioned to expect an electric shock or made hyperactive by means of septal lesions (Bainbridge and Greenwood 1971). D,L-propranolol, and in higher doses also D-propranolol, reduces exaggerated exploratory behaviour in rats reared in isolation (Speizer and Weinstock 1973). The increased motor activity induced in rats by amphetamine is suppressed by D,L-propranolol and D,L-oxprenolol (Weinstock and Speizer 1974). The stereotyped behaviour following administration of methamphetamine is suppressed by propranolol (Estler and Ammon 1971). Intraperitoneal oxprenolol and metoprolol modify the delayed differentiation behaviour of macaques (Clancy et al. 1977). D,L-propranolol disrupts the performance of rats in a 'differential reinforcement of low rates responses' design (Richardson et al. 1972), whereas the same drug and pronethanol were found to improve learning of a conditioned avoidance response in rats (Merlo and Izquierdo 1971). Using ethological and individual behavioural parameters in grouped monkeys, it has been shown that propranolol and oxprenolol possess tranquillizing and anxiolytic properties; they reduce aggressiveness and increase social contacts (Koella 1978). The tremorin-induced tremor of mice is suppressed under the influence of the β-blockers sotalol, propranolol, dichlorisoproterenol (DCI) and pronethanol; whereas tremor induced by physostigmine is unaffected by β-blockers (Sharma et al. 1971). Convulsions induced by electroshock, pentetrazol, or strychnine are reduced or completely suppressed by propranolol and similar drugs (Yeah and Wolf 1968; Madan and Barar 1974).

The electrographic arousal reaction in gallamine-immobilized cats, induced by electrical stimulation of the mesencephalic reticular formation or of the locus coeruleus, is markedly reduced in extent and duration by D,L-oxprenolol and D,L-propranolol administered intravenously or applied locally to the exposed cortex (Koella 1977, 1978; Dillier et al. 1978). According to Hilakivi and co-workers (1978) propranolol (5 mg/kg) and pindolol (0.1–0.5 mg/kg i.p.) enhance sedated drowsy waking and reduce (deep) slow-wave sleep. Propranolol also significantly reduces paradoxical (REM) sleep.

With this evidence there can be little doubt that β-blockers, in one way or the other, affect the activity of, and output from, a number of central nervous structures or 'systems'. With future generations of β-blockers to be used to combat peripheral disorders, one would be interested in a reduction of the above mentioned undesirable side-effects. In turn, central therapeutic efficacy should be improved if these β-blockers are to be used to treat central nervous diseases. Improved therapeutic efficacy of β-blockers used to treat peripheral autonomic disorders may be achieved by supplementing the peripheral action with an additional central component. Yet the success of such endeavours depends on our proper understanding of the mechanism and locus of action by which β-blocking agents exert central influences. It is here that one encounters several complications. A closer look at the types of central effects obtained with various types of β-blockers clearly indicates that the sum-total of these drug-induced changes in central activity cannot be explained by one common and uniform mechanism at one locus of action only. A multitude of mechanisms at a variety of loci must be considered. As a first step, theoretical models of these different mechanisms can be construed on the basis of the characteristics of the 'effects' and of the dosage used. Experimental evidence can then be used with these theoretical schemes to create realistic models. In the next section we shall delineate the more important mechanisms, based on the procedures and principles discussed previously (Koella 1977, 1978).

Mechanisms through which β-Blockers may Affect the CNS

Centrally Mediated Specific β-Adrenergic Mechanism

It is assumed that β-blockers which penetrate into the brain (i.e. into the space enclosed by the blood-brain barrier, BBB) in sufficient amounts, bind to β-adrenergic receptors, suppress information flow in noradrenergic β-receptor-mediated channels, and change activity (or reactivity) in a variety of networks under β-adrenergic control. Such a mechanism would explain some of the behavioural and neural effects produced by the racemic or the active stereoisomeric form of highly lipophilic β-blockers. However, one should be aware that a partial agonist component is liable to distort this relatively simple pattern of action. The pattern of deactivation of β-ad-

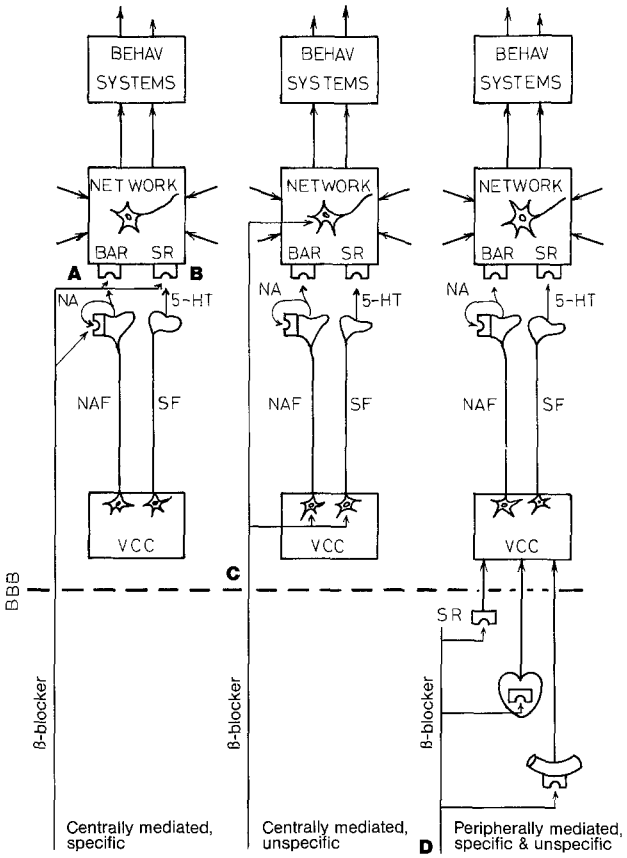

Fig. 1. Schematic representation of the four major mechanisms and loci of action of β-blocking agents involved in the production of the various side- and therapeutic effects. The left-hand column combines A, the centrally mediated specific β-adrenergic mechanism and B, the centrally mediated specific serotonergic mechanism. The middle and the right-hand columns depict C, the centrally mediated non-specific mechanism and D, the peripherally mediated mechanism. Non-specific mechanisms (via membrane-stabilization) are assumed to act via attack at 'sensitive' aminergic cells in the vigilance-controlling centre (VCC, assumed to be located in the rhomb-, mes-, and diencephalic reticular formation) and/or (less likely) at cells in the effector-networks. Abbreviations: BAR = β-adrenergic receptors; SR = serotonergic receptors; NAF = noradrenergic fibre; SF = serotonergic fibre; BBB = blood-brain barrier. The small arrows pointing towards the 'networks' indicate the steering and organizing inputs to these behaviour-producing neuronal systems.

renergic transmission can be complicated further by the additional involvement of presynaptically located β-receptors (Adler-Graschinsky and Langer 1975; Stjärne and Brundin 1975) which if activated, facilitate, and if blocked inhibit, release of noradrenaline from noradrenergic nerve terminals and varicosities.

Centrally Mediated Specific Serotonergic Mechanism

It is assumed that β-blockers which penetrate into the intra-BBB-space, bind with high-affinity to *non*-adrenergic receptors, interfere with the proper signal flow in *non*-adrenergic pathways, disturb the activity (and reactivity) in networks controlled by such pathways, and thus disturb the behavioural activities organized by these networks. There is evidence (Middlemiss et al. 1977; 1981) that propranolol, oxprenolol, alprenolol and pindolol, but not practolol and atenolol, stereospecifically bind to serotonin-receptors to act as 5-HT-receptor antagonists.

Centrally Mediated Non-specific Mechanism

It is assumed that β-blockers which penetrate into the intra-BBB-space, silence some especially sensitive neurones in the CNS due to their membrane-stabilizing characteristics, thus interfering with proper activity of the networks containing such neurones, and therefore disrupt the behavioural activity organized by these networks. This mechanism would explain effects produced by the inactive stereoisomeric form of some β-blockers.

Peripherally Mediated Mechanism

It is assumed that by interruption of, or partial agonism towards, β-adrenergic pathways, and/or via their local anaesthetic action, β-blockers would produce the well established changes in activity of peripheral, mainly autonomic effector systems. Information about such changes is signalled through neuronal and/or humoral pathways to the CNS, where it induces reflex-changes in the activity (or reactivity) in some selected central networks which, in turn, result in changes in the behavioural and neural activities organized by these networks. These four mechanisms are depicted schematically in Fig. 1.

It is safe to assume that the relative weight with which any of these four mechanisms of action modifies behavioural and/or neural effects depends on the characteristics of the β-blocker: transport and metabolic kinetics, partition coefficient, receptor affinity, ratio of antagonist versus agonist qualities, affinity to non-adrenergic receptors, strength of membrane-stabilizing properties, and on the dose and route of administration. Furthermore, proper interpretation of the effects produced by a β-blocker and its involvement in these mechanisms must be based on knowledge of physiological function(s) and properties of the 'substrates' or 'systems' through which the mechanisms are effective.

Concerning the *centrally-mediated specific mode of action,* it is assumed that through their antagonistic and possibly agonistic action, β-blockers interfere with the normal but variable information flow in central noradrenergic (NA) and possibly adrenergic

pathways. The ascending (and descending) NA fibres that constitute these pathways arise in a group of nuclei of the midbrain, the pons (mainly the locus coeruleus), and the medulla. The NA fibres project, in a widely diverging manner to the anterior brain stem, to most parts of the limbic system, and to almost all areas of the cerebral (neo-)cortex. Experimental evidence suggests that mainly through β-adrenergic channels NA fibre systems exert an activating influence on cerebrally organized behavioural functions (Koella 1982, 1984). Well designed experiments indicate that the NA pathways, through projections to the neocortex and limbic system, enhance responsiveness (mainly but not exclusively) in those systems that handle higher functions. When rat central NA pathways are poisoned by local injection of 6-OHDA the frequency of cortical EEG is reduced without greatly affecting motor activity (Lidbrink 1974; Matsuyama et al. 1973). Presynaptically selective α_2-receptor agonists, such as clonidine, reduce NA release, impair orienting behaviour, and reduce signs (of high 'local reactivity') of paradoxical sleep in rats and cats (Kleinlogel et al. 1975; Leppävuori and Putkonen 1980). Lesions of the locus coeruleus are followed by a reduction of the learning speed (Anlezark et al. 1973). Interruption of the coeruleocortical NA fibres increases resistance to extinction (i.e. impairs a specific type of learning) of a previously learned runway response (Mason and Iversen 1975). Depletion of cerebral cortical NA by infusing 6-OHDA into the dorsal bundle impairs the ability of rats to ignore irrelevant stimuli (Mason and Fibiger 1979). In turn, a specific increase in NA concentration at synaptic sites, as induced by preferential α_2-blockers such as yohimbine or piperoxan, prolongs waking time and enhances the signs of paradoxical sleep in rats and cats (Leppävuori and Putkonen 1980; Kafi and Gaillard 1981). NA injected into the hypothalamus or the (rostral) ventricular space enhances the orienting activity of rats (Benkert and Koehler 1972; Geyer et al. 1972; Segal and Mandell 1970). Electrical stimulation of the locus coeruleus (LC), the point of origin of the dorsal NA-bundle, is followed by electrocortical, behavioural and ergotropic-autonomic signs of arousal, not unlike the pattern produced by stimulation of the midbrain reticular formation. Interestingly, it has been shown that this stimulation can be antagonized by systemic and, as far as the cortical signs of arousal are concerned, by local application of β-blockers (Koella 1978). Redmond et al. (1976) have demonstrated that electrical stimulation of the LC of monkeys elicits an alerting response.

In the light of a novel "General theory of vigilance" proposed by Koella (1982) we can postulate that noradrenergic, probably β-receptor-mediated, signals enhance the local reactivity in those neuronal networks that are responsible for the organization of higher functions, and thus enhance (local) vigilance in the respective behavioural systems. Evidently, enhanced NA activity comes into play to 'prepare the systems' for proper performance of all those higher-function activities that fill the waking period. NA-fibres also have to be active, although probably to a lesser degree, during paradoxical sleep, for the enhancement of reactivity in those (cortical and limbic) networks that have to be responsive for the experiencing and 'learning' of dreams.

If we accept that β-blockers interact with transmission activity in central adrenergic pathways, we are able to interpret some of the β-blocker-induced symptoms as manifestations of reduced vigilance in a variety of (mainly higher function) behavioural systems. This should be evident during waking as sedation and during REM sleep as a suppression of the typical behavioural signs of this phase of sleep.

A similar case, mutatis mutandis, can be made for that component of the effect of some β-blockers that derives from their additional affinity towards 5-HT-receptors. Much evidence indicates that serotonergic transmission channels - antagonists to the noradrenergic (and cholinergic and dopaminergic) channels - are the main reactivity-suppressing mechanisms (Koella 1982, 1984). Serotonergic channels counteract excessive arousal and enforce the low level of vigilance during slow-wave sleep. The effect of such 5-HT-active β-blockers should consist mainly of a reduction of the signs of slow-wave sleep (including reduction of growth hormone output as reported by Charney et al. (1982)) in addition to a lowered anti-arousal efficacy.

Concerning the *centrally mediated non-specific mode of action*, little can be said about the systems affected by inhibition of central neurones owing to the membrane-stabilizing effect of β-blockers. At this time we have little evidence as to the types of specially sensitive central nerve cells that would be susceptible to such non-specific drug action. In view of the obvious similarity between the effects of active and of inactive (D-forms) β-blockers, one supposes that the small aminergic neurones (NA, 5-HT, but also DA and ACh) would be the main targets of this local anaesthetic influence.

Concerning the *peripherally mediated mode of action* there is some evidence about putative mechanisms involved in the transmission of peripherally (i.e. extra-BBB) induced changes towards the CNS. The results of experiments in man and animals designed to investigate the central effects of non-penetrating β-blockers are not unequivocal. There is posi-

tive evidence for such indirectly produced central effects (Bonn and Turner 1971; Bonn et al. 1972; Speizer and Weinstock 1973), but others have found no evidence for such action (Estler and Ammon 1969; Engel and Liljequist 1976). Possible mechanisms and pathways that could carry information about peripheral effects of such drugs to the CNS so inducing central symptoms, are discussed below. A search for such mechanisms is appropriate also in view of the claim that the anti-anxiety effect of β-blockers is peripherally mediated (Tyrer 1980).

Centripetal transmission is well documented by subjective experiences of anxiety due to peripheral malfunction, unless one is ready to concede that conscious experiencing is entirely accomplished in the periphery! It is well known that exaggerated autonomic activity in the periphery, such as palpitations of the heart and other peripheral sources of discomfort, can induce a marked degree of anxiety. It is more than likely that afferent fibres of the autonomic nervous system are involved in the centripetal transmission of such information. A reduction of such peripheral activity by, say, hydrophilic β-blockers, is in turn able to reduce the extent of afferent information and to reduce the feelings of anxiety.

Yet there is also experimental evidence to put such subjective and clinical findings on a more scientific basis, because it suggests some discrete mechanisms that could be involved in centripetal transmission and therefore in the production of certain activity patterns in the CNS. An increase in pressure within the carotid sinus leads to a shift in the cortical EEG towards lower frequencies and to changes in the amplitude of evoked potentials (Bonvallet et al. 1954; Koella et al. 1960). In turn, lowering of intrasinusoidal pressure is followed by electrographic signs of enhanced arousal (i.e. elevated cortical vigilance). While such effects, probably transmitted via the solitary tract nucleus, are opposite to the effects expected, they nonetheless demonstrate the principle of mechanisms that effect transmission of peripheral information to the CNS, and induce changes in activity of central nervous structures. However, there is also evidence that an increase in intracranial intravascular pressure enhances arousal (Baust et al. 1962a,b). From this evidence one concludes that a reduction in intra-arterial pressure within the cranium will reduce arousal, i.e. reduce the level of vigilance in a variety of behavioural systems. Such a mechanism will be significant if exaggerated levels of vigilance are curtailed by the hypotensive effect of β-blockers.

Furthermore, there is evidence that the CNS contains aminergic receptors which are situated outside the blood-brain barrier. Thus it has been shown that the area postrema, which lies outside the blood-brain barrier, or a site close by contains 5-HT receptors (Koella and Czicman 1966; Roth et al. 1970). Serotonin applied directly to the area postrema or injected into the artery supplying this structure, interacts with these receptors and, through an increased amplification in the solitary tract nucleus, produces enhanced inhibitory (reticulo-solitario-reticular) feedback to the activating part of the reticular formation. This feedback generates an 'antiwaking' effect (Koella 1974) or, in more modern terms, a reduction of vigilance (Koella 1984). It is not unlikely that β-blockers, if they include a 5-HT-receptor blocking activity, could interact with this serotonin-modulated feedback loop and release vigilance-enhancing mechanisms from their normal inhibitory influence.

Interpretations

In the previous sections we have developed models of the four most relevant and important mechanisms of action through which β-blockers can be assumed to produce their central side-effects and therapeutic activity. Information is also available concerning the functional characteristics and roles of some of the substrates or systems affected by these agents when generating these central effects. We can proceed to interpret the side-effects and therapeutic activity produced by different β-blockers, in terms of mechanisms involved, in order to test our hypotheses.

Central effects are assumed to be greater and more frequent with lipophilic than hydrophilic agents. However, with hydrophilic drugs some influence on central activity is observed. This strongly indicates that the centrally mediated (specific or non-specific) mode of action is more powerful than the peripherally mediated mechanisms although the magnitude of the centrally mediated action depends on the level of penetration into (i.e. the concentration of the drug within) the intra-BBB-space. In turn, it is expected that the inhibition of postsynaptic receptors, and thus the true block of forward information flow, is further accentuated by the interaction of the β-blockers with presynaptic β-adrenergic receptors, by curtailing release of the transmitting vehicle. A further reason for the considerably stronger central effects of lipophilic agents is apparent when one considers that with the penetrating lipophilic β-blockers the centrally mediated and the peripherally mediated influences should be additive, whereas with hydrophilic agents there is only peripheral action. This assumes that the two mechanisms result in effects of similar nature and direction.

Furthermore, animal experiments have shown that inactive stereoisomers of, for instance propranolol, although able to produce qualitatively similar effects, are considerably less potent than the active L-isomer. This is probably because the membrane-stabilizing action is not very efficient in producing changes in central nervous activity, and/or that the local threshold concentrations necessary to influence efficiently the cell membranes are not reached, unless large doses are given. However, one should remember that with respect to local anaesthetic action, lipophilic agents are more potent than hydrophilic ones (see, e.g., Koella 1978).

Sedation

Sedation and drowsiness are often seen as side-effects of lipophilic β-blockers and probably result from a multitude of mechanisms. First, this sedating effect can be interpreted as a manifestation of a post- and presynaptically effected suppression of signal flow in central noradrenergic vigilance-enhancing areas. Second, the effect of this central specific mechanism is probably supported and intensified by a central non-specific component. Third, the (peripherally) β-blocker-induced reductions in blood pressure and, thus, intracranial intravascular pressure are liable to intensify further central deactivation, via the pressure-sensitive component of the reticular formation (Baust et al. 1962a, 1962b). However, this effect may be somewhat attentuated by negative feedback arising in the carotid sinus and aorta (Koella et al. 1960). Fourth, feelings of fatigue and drowsiness may be the consequence of an accumulating sleep deficit caused by the sleep disturbance often noted with mainly lipophilic β-blockers.

Tranquillizing and Anxiolytic Properties

The direct specific and unspecific, as well as the indirect mechanisms are likely to mediate tranquillizing and anxiolytic effects when β-blockers, mostly of the lipophilic type, e.g. propranolol, are used as therapeutic agents. Again, central β-receptor blocking effects play a major role. This interpretation is supported by the findings of Margules (1971) who has demonstrated that the punishing effect of (painful) electrical foot stimulation on operant behaviour (a manifestation of anxiety) is mediated in the amygdaloid nucleus by β-adrenergic transmission pathways. Suppression of such transmission activity by directly acting β-blockers should reduce this anxiety. In addition, if adequate intra-BBB concentrations can be attained, a direct non-specific mode of action may become effective. Also, a peripheral influence by β-blockers may act as an antianxiety factor, through reduction of peripheral autonomic (over-)activity. Some authors argue that this peripheral mechanism appears to be the major anxiolytic action (Tyrer 1980).

Sleep Disturbances

The interpretation of the mechanisms of action involved in the β-blocker-induced sleep disturbances requires separate consideration of several components of this side-effect. A priori, one would expect that inhibition of β-adrenergic transmission in the major central vigilance-enhancing pathways would facilitate the onset of sleep. However, this is not the case because this factor appears to account only for a degree of central deactivation, but not for the induction of true sleep. This was established in the animal experiments of Hilakivi and co-workers (1978). These authors observed that although waking time was increased in cats receiving propranolol or pindolol, this waking state was of the drowsy variety, i.e. a state revealing signs of lowered vigilance. This effect is adequately explained by the central specific (i.e. β-adrenergic blocking) action of the lipophilic β-blockers. This action may be supported and intensified by additional, e.g. central non-specific or even peripheral, mechanisms. A central β-adrenergic blocking effect is assumed to be mainly responsible for the reduction of the signs of REM-sleep, as observed in cats by Hilakivi et al. (1978) and in man by Betts and Alford (1985). There is ample evidence (Koella 1984) that enhanced local vigilance in systems of higher and lower functions during periods of paradoxical sleep is the result of intensified activity in the mainly β-adrenergic pathways impinging on those systems. A suppression of β-adrenergic transmission (produced by, e.g. propranolol) or a reduction of NA-release (produced by, e.g. clonidine) will prevent elevated vigilance. However, β-blockers also reduce NREM-sleep, in particular its deeper stages 3 and 4. Slow-wave sleep is characterized mainly by markedly reduced reactivity and vigilance in functions organized by the cerebral neocortex and limbic system. Electrographically this is well documented by the pronounced occurrence of the slow delta-waves in the cortical EEG, and, together with a loss of theta-activity, in the limbic system, e.g. the hippocampus. There is much experimental evidence that serotonergic pathways are responsible for reactivity- and vigilance-suppression (Koella 1984). Thus NREM-3- and NREM-4-insomnia are adequately explained by a suppression of serotonergic transmission at the (intra-BBB) projection sites of the 5-HT-pathways, i.e. by the affinity to, and the antagonism toward, 5-HT-

receptors of (mainly lipophilic) β-blockers, as demonstrated by Middlemiss and co-workers (1977). Furthermore, it is not unlikely that the effect of a block of intra-BBB serotonergic transmission is supplemented by a similar block of the 5-HT-receptors at the area postrema (outside the BBB) and the consequent reduction in inhibitory feedback activity impinging on the activating reticular formation (Koella and Czicman 1966).

Concerning the explanation of the heightened incidence of nightmares in response to (preferably lipophilic) β-blockers, we can agree with the interpretation of Betts and Alford (1985) that premature awakening immediately after a dream and thus, the elimination of the 'memory-erasing' NREM-sleep, will increase the probability that dreams, good or bad, are remembered. In addition to this operational explanation, we would propose that the β-blocker-induced obvious imbalance and faulty coordination between the various aminergic pathways and the consequent lack of checks may constitute an additional factor for the emergence of affectionally loaded dreams. Again, the relative lack of the damping and antiarousal serotonergic influence (Trulson and Jacobs 1979) may be a major factor here.

Hallucinations, Drug Abuse and Alcoholism

Similar reasoning may explain the production of hallucinations. The hallucinogenic properties of LSD-25, the classical psychodelic drug, derive from its ability to interfere with serotonergic and dopaminergic transmission (Freedman and Halaris 1978). The hallucinogenic (and outright psychotogenic) properties of some β-blockers may also be due to a derangement in the output from, and the balance between, some aminergic mechanisms. As this side-effect is rather rare, one must postulate a particular predisposition in some part of the patient population towards the manifestation of this side-effect.

However, if one accepts this explanation for the mechanisms of action by which β-blockers induce hallucinations, it becomes more difficult to explain the proposed, although not unchallenged, antischizophrenic properties of these agents. One may speculate that this obvious reversal of the effect is due to the astonishing increase in dose, by at least one order of magnitude, which is necessary to accomplish antipsychotic efficacy.

Finally, we are completely unable to explain the mechanisms of therapeutic action of β-blockers used to combat drug abuse, withdrawal symptoms, alcoholism, or certain types of tremor. We can only hope that future research will furnish the necessary basis for a better mechanistic interpretation of these effects. Such experimental results will be instrumental also in improving the interpretations of those effects discussed earlier in this paper, for which we had to revert to speculation, rather than to fact, to explain the mechanisms involved in producing the therapeutic action and undesirable side-effects of β-blockers.

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Group Discussion

P. A. van Zwieten

It has been proposed that 5-HT-receptors may be involved in nightmares. Is this a realistic proposal? Do the 5-HT-blockers used to treat migraine produce these side-effects?

W. P. Koella

Antimigraine drugs such as methysergide and cyproheptidine are known to cause sleep disturbances, but we can only speculate that these side-effects are related to blockade of 5-HT-receptors.

R. Fiocchi, University Hospital St. Raphael, Gesthuisberg 3000 Leuven, Belgium

Is the permeable part of the area postrema involved in controlling mood or sleep disturbance? If this is so, is it possible that drugs which do not normally penetrate the brain may affect mood if they pass into the permeable part of the area postrema?

W. P. Koella

We have very little indication that activation of receptor sites in the area postrema does affect mood. But as we find a feedback line from this structure (via the solitary tract nucleus) to the reticular formation, it is not impossible that mood, or vigilance in some 'mood systems' is controlled from this extra-BBB organ.