Biochemical Pharmacology, Vol. 32, No. 10, pp. 1539–1545, 1983.
Printed in Great Britain.

0006-2952/83 $3.00 + .00
Pergamon Press Ltd.

COMMENTARY

PHYSIOLOGICAL AND PHARMACOLOGICAL ASPECTS OF ADRENERGIC RECEPTOR CLASSIFICATION

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Abstract—The questions raised are: what is the physiological or pharmacological basis for the differentiation into β_1- and β_2-, and α_1- and α_2-adrenergic receptors?; and do the neurotransmitter norepinephrine and the hormone epinephrine differ in their receptors? On the basis of a preference of β_2- and α_2-adrenergic receptors for epinephrine, the hormone, and of β_1- and α_1-receptors for norepinephrine, the neurotransmitter, it was postulated that the α_2- and β_2-receptors are predominantly epinephrinergic in nature and located extrajunctionally and presynaptically whereas the α_1- and β_1-receptors are predominantly norepinephrinergic in nature and located postsynaptically in the sympathetic terminal junction. The α_2- and β_2-character of the presynaptic receptors matches that of the corresponding extrajunctional receptors. This indicates that a circulating catecholamine, namely epinephrine, is involved in the regulation of adrenergic transmitter release.

Receptorology is the discipline involved in the study of the molecular mechanisms operative in inter- and intracellular chemical communication at the level of the receptor molecules. These molecules have a capability to select particular chemical messengers, to read the message and to translate it into receptor activation which then, via a receptor–effector coupling, is transferred to the effector system concerned. The field of receptorology is extremely wide. It comprises receptors dealing with chemical messengers such as neurotransmitters (acetylcholine etc.), mediators (histamine etc.), hormones (steroids, peptides etc.), allosteric activators and inactivators of enzymes in biochemical feed-back controls, repressor and derepressor molecules which control biochemical processes at the level of chromosomal DNA, immunoreceptors etc.

Receptor differentiation

As a matter of fact, for the different chemical messengers different receptors—receptor molecules differing in receptor sites—will exist. Sometimes, for one chemical messenger different types of receptors have to be distinguished, such as the α- and β-adrenergic receptors, the H_1- and H_2-histamine receptors and the D-1- and the D-2-dopamine receptors. In these cases there is a clear-cut difference in the receptor–effector coupling; β-adrenergic, H_2-histamine and D-1-dopamine receptors, for instance, are coupled via the second messenger cyclic AMP whereas α-adrenergic and H_1-receptors are coupled via cyclic GMP and/or Ca^{2+}. Often the corresponding blocking agents give a sharper differentiation between the receptor types mentioned than the agonists. Another aspect of receptor differentiation is a difference in location. The cholinergic (muscarinic) receptors at the vagal nerve endings and the cholinergic (nicotinic) receptors at the myoneural junction may exemplify this. There are no indications for differences in receptor–effector coupling in this case. What may count is the influence of the environment, the constitution of the membrane, on the properties of the cholinergic receptor protein embedded therein.

Intriguing is the differentiation between β_1- and β_2-adrenergic receptors by Lands *et al.* [1, 2] and between α_1- and α_2-adrenergic receptors by Langer [3] and Starke [4] on the basis of a specificity in the chemical agents capable of activating or blocking the respective receptors. There is no indication of a difference in receptor–effector coupling for β_1- and β_2- or α_1- and α_2-receptors, but there are indications of a difference in the distribution of these receptor types in various organs. Analogous relationships arise for α_1- and α_2-sensitivity [6, 7]. It is a challenge to search for the physiological and pharmacological background of this receptor differentiation.

Receptors for the neurotransmitter norepinephrine and the hormone epinephrine and their relation to α_1- and β_1 and to α_2- and β_2-adrenergic receptors, respectively

In an historical overview, Bacq [8] discussed the trials and errors around the classification of the 'sympathins', finally leading to the recognition of norepinephrine as the predominant mammalian sympathetic neurotransmitter and epinephrine as the sympathetic hormone. There is a good deal of analogy in the struggle around the classification of the 'sympathins' and that of their receptors. The differentiation between the neurotransmitter norepinephrine and the hormone epinephrine essentially contributes to the physiological and pharmacological interpretation of the various adrenergic receptor types. Since norepinephrine and epinephrine differ chemically as well as in their effects, it may be assumed that they also differ in their specific receptor systems. Optimal mutual adaptation between the messengers and their specific receptor sites may be expected to have taken place through the eons of evolution.

Two questions arise.

(1) What is the physiological or pharmacological

basis for the differentiation into β_1- and β_2-, and α_1- and α_2-adrenergic receptors?

(2) Do the neurotransmitter norepinephrine and the hormone epinephrine differ in their receptors?

A solution to these two questions may possibly be found in one answer, namely the postulate by Ariëns and Simonis [9] that the β_1- and α_1-receptors are postsynaptic junctional receptors for the neurotransmitter norepinephrine released as the sympathetic nerve endings and the β_2- and α_2-receptors are extrajunctional receptors, particularly sensitive to the hormone epinephrine, at least in mammals and outside the CNS [10–12]. Carlsson and Hedberg [13, 14] presented a similar hypothesis indicating β_1- as possible 'innervated' and β_2- as 'hormonal' β-adrenoceptors. Circumstantial evidence for the hypothesis, extended also to prejunctional α_2- and β_2-receptors, will be presented.

β_1- and β_2-adrenergic receptors

Over the past years various arguments in favour of this postulate have been generated with regard to β_1- and β_2-receptors. Carlsson *et al.* [15] reported that in the isolated cat heart the effects of norepinephrine are preferentially blocked by the β_1-blocker practolol, and those of epinephrine by the β_2-blocker H35/25, whereas the β_1–β_2-blocker propranolol is about equally effective against both catecholamines. The chronotropic responses in the heart of the anaesthetized cat induced by norepinephrine or sympathetic nerve stimulation appear to be much more sensitive to the β_1-blocker practolol than the responses induced by epinephrine [14, 16, 17].

The differentiation into β_1- and β_2-adrenergic receptors by Lands *et al.* [1, 2] has resulted in a classification of tissues into β_1-adrenergic tissues, such as the adipose tissue (lipolysis), the jejunum (relaxation) and the heart (force and rate), and tissues predominantly β_2-adrenergic in nature such as striated muscle (lactic acid production), the uterus (relaxation) and the bronchial tree (relaxation), as summarized in Table 1 [5]. The vasodilatation in striated muscle is considered to be the result of the lactic acid production induced on β_2-receptors in the muscle cells.

Table 2 [18–21] summarizes the relative sensitivity (epinephrine/norepinephrine) of various tissues. Putting the tissues in order of this relative sensitivity results in the sequence given in Table 2. A comparison of Tables 1 and 2 shows that the classification into predominant β_1- and β_2-organs closely correlates with that on the basis of the sensitivities for the neurotransmitter norepinephrine and the hormone epinephrine. The tissues classified as β_1-adrenergic are particularly sensitive to norepinephrine and those classified as β_2-adrenergic are particularly sensitive to epinephrine.

This suggests a relation between β_1-receptors and the neurotransmitter, and between β_2-receptors and the hormone. Both striated muscle (diaphragm) and uterine smooth muscle, which are reported to be poorly sensitive to the neurotransmitter norepinephrine (Table 2), are almost purely of the β_2-type (Table 1) and are known to have little or no sympathetic innervation [22–24]. As demonstrated by Furchgott *et al.* [25] and by other investigators [26, 27], β_1- and β_2-receptors occur side by side and in varying proportions in various tissues.

An interesting aspect of the data in Table 2 is that the frog heart falls into the range of the β_2-adrenergic organs; it is particularly sensitive to epinephrine. This does not correspond to the classification of the (mammalian) heart as β_1-adrenergic (Table 1). This apparent deviation, however, fits in very well with the concept under discussion since, in contrast to mammals, where norepinephrine serves as the sympathetic neurotransmitter, epinephrine is the transmitter in the sympathetic system in the frog and toad [28–31]. Thus, the β_2-adrenergic character of the frog heart fits in quite well with epinephrine being the neurotransmitter there.

As a consequence, in general it is correct to classify β_1-adrenergic receptors as sites of action for norepinephrine and β_2-adrenergic receptors as sites of action for epinephrine, whereas the denomination neurotransmitter, or 'innervated', and hormonal, or 'humoral', adrenoceptors then holds true for mammalians but not, for instance, for the frog and toad, and possibly for other species [32].

In most organs, neurotransmitter, junctional, β_1-receptors as well as hormonal, extrajunctional, β_2-receptors are found, although the ratios for the β_1-/β_2-receptor capacities largely differ for various organs and tissues [29, 33–37]. The distribution of the β_1-receptors, the junctional receptors, may be expected to be related to the density of sympathetic

Table 1. Correlation of rat muscle glycogenolysis (β_2-adrenergic) with various β_1- and β_2-adrenergic receptor responses to catecholamines

Rat muscle glycogenolysis vs	N	Correlation coefficient
β_1 Rat adipose tissue lipolysis	9	0.061
Guinea pig adipose tissue lipolysis	6	<0.001
Rabbit jejunum inhibition	7	0.108
Rabbit heart force	8	0.215
Rabbit heart rate	8	0.227
β_2 Rat diaphragm contraction	7	0.960
Rat uterus inhibition	8	0.982
Guinea pig bronchodilatation	9	0.971
Dog vasodepression	9	0.931

After Arnold and Selberis [5].

Table 2. Relative activity of epinephrine and norepinephrine on different organs in relation to their characterization as far as β_1- and β_2-adrenergic character is concerned

Biological object	Species	Pretreatment		Relative activity (epinephrine/norepinephrine)	β_1/β_2	Ref.
		Coc.	α-bl.			
Atrium (force)	Guinea pig	+		0.5	$\beta_1 > \beta_2$	[20]
Atrium (force)	Rabbit	+	+	0.5	$\beta_1 > \beta_2$	[20]
Atrium (frequency)	Guinea pig	+		0.2	$\beta_1 > \beta_2$	[18]
Atrium (frequency)	Rabbit			0.6	$\beta_1 > \beta_2$	[19]
Duodenum	Rabbit	+	+	0.2	$\beta_1 > \beta_2$	[20]
Duodenum	Guinea pig	+	+	0.5	$\beta_1 > \beta_2$	[20]
Duodenum	Human	+	+	0.6	$\beta_1 > \beta_2$	[21]
Jejunum	Rabbit			0.35	$\beta_1 > \beta_2$	[19]
Caecum	Mouse	+		0.3	$\beta_1 > \beta_2$	[18]
Stomach (fundus)	Rabbit	+	+	1.2	$\beta_1 \simeq \beta_2$	[20]
Stomach (fundus)	Human	+	+	2.7	$\beta_1 \simeq \beta_2$	[21]
Colon	Guinea pig	+		2	$\beta_1 \simeq \beta_2$	[18]
Colon (longitudinal)	Human	+	+	3	$\beta_1 \simeq \beta_2$	[21]
Trachea	Calf	+		8	$\beta_2 > \beta_1$	[18]
Trachea	Guinea pig	+	+	12	$\beta_2 > \beta_1$	[20]
Uterus	Rat			103	$\beta_2 \gg \beta_1$	[19]
Diaphragm	Rat			111	$\beta_2 \gg \beta_1$	[19]
Lactic acidemia	Rat			145	$\beta_2 \gg \beta_1$	[19]
Heart	Frog			42	$\beta_2 \gg \beta_1$	[18]

Coc. = cocaine.
α-bl. = α-adrenergic blocker.

innervation of the organ or tissue. Tissues without sympathetic innervation are found to contain, as expected, practically exclusively β_2-, extrajunctional, receptors. So, for instance, erythrocytes [38], lymphocytes [39], mast cells [40], polynuclear neutrophiles [41], uterine smooth muscle [22, 23] and striated muscle [24, 42] are classified as β_2-adrenergic in nature. Further arguments pro and contra the hypothesis may be obtained from studies on indirectly acting sympathomimetics. Such agents, e.g. tyramine, the action of which is based on the presynaptic release of transmitter norepinephrine, are expected to cause predominantly β_1-effects, and to be blocked by β_1-blockers. Tyramine is reported to induce β_1-effects on the heart but no effects on striated muscle or uterine muscle are to be expected. Blockade of the neuronal reuptake of neurotransmitter by agents such as cocaine should potentiate the effects induced on β_1-receptors more clearly than those induced on β_2-receptors. The effect of nicotinic (ganglionic) or direct sympathetic stimulation in the absence of the adrenal medulla should be mostly β_1-adrenergic in nature. The up-regulation in adrenergic receptor density after sympathetic denervation [43, 44] may be expected to be more pronounced for β_1-adrenergic receptors.

Since receptor blockers can only manifest their action in the presence of an agonist activating the corresponding receptors, the selectivity in blocking capacity for β_1- or β_2-blockers will depend on the degree to which the neural sympathetic (norepinephrine) or the hormonal adrenal (epinephrine) systems are operative. Under basic conditions, the neural sympathetic system is continuously involved in cardiac and vascular circulatory regulation for maintenance of homeostasis. The hormonal (epinephrine) system is predominantly operative under physical and psychical stress—the 'fight, fright, flight' reaction. This implies that under basic conditions the characteristics of β_1-receptor blocking agents, for instance metoprolol, and those of β_1–β_2-receptor blocking agents, for instance propranolol, can hardly be differentiated. Activity on the level of both the sympathetic nerve system (norepinephrine) and the hormonal system (epinephrine) is required. In clinical studies on the circulatory effects, the expected differences between the β_1–β_2-blocker propranolol and the β_1-blocker metoprolol do not become manifest under basic conditions but they do under conditions of heavy physical stress and especially if epinephrine is infused—which means that the hormone is substituted then [16, 45–47].

In the CNS there is also a differential distribution of β_1- and β_2-adrenergic receptors [30, 48–50]. The results of surgical and chemical central noradrenergic denervation are of particular interest, here. Dorsal norepinephrine bundle lesions doubled the number of cortical β_1-receptors but did not alter the number of β_2-receptors [51]. In newborn rats, 6-hydroxydopamine, which destroys noradrenergic terminals, caused an increase in the density of β_1-adrenergic receptors, while the density of β_2-receptors did not change [52]. The up-regulation is restricted to the β_1-adrenergic receptors. This argues for a relationship between noradrenergic nerve terminals and thus between the neurotransmitter norepinephrine and β_1-adrenergic receptors. Such a relationship was to be expected on the basis of the hypothesis.

The concept of junctional, preferentially norepinephrine-sensitive β_1-adrenergic receptors and extrajunctional preferentially epinephrine-sensitive β_2-adrenergic receptors is gradually breaking through in the literature [17]. Zaagsma *et al.* [37] conclude from a study on β-adrenergic receptors in

the pulmonary system that "it seems justified to assume β_1-adrenergic receptors in the respiratory tract to be noradrenergic neuronal receptors, and the β_2-receptors to be adrenergic humoral receptors". They report [53] that in a comparison of guinea pig trachea, main bronchus and intrapulmonary airway tissue the apparent affinity of norepinephrine (in the presence of cocaine) dramatically decreases in that direction, parallel to a decrease in β_1-adrenoceptors, which are no longer present in the fine peripheral airways of the lung. O'Donnell *et al.* [54] report that in the same direction the density of sympathetic innervation in the guinea pig lung decreases. For the human lung both centrally and peripherally only a homogenous β_2-adrenoceptor population is found [53]. Richardson [55] has established that in humans no functional adrenergic innervation is present in tracheal and bronchial smooth muscle or in the lungs. Bryan *et al.* [56] reported in their paper on 'innervated and hormonal β-receptors' that their findings especially in relation to extraneuronal and neuronal uptake of catecholamines are in accordance with the hypothesis. Extraneuronal uptake of catecholamines does not operate in tissues having only β_1-adrenoceptors. Hawthorn and Broadley [57] conclude on the basis of differences in the effect of inhibitors of neuronal uptake of catecholamines with regard to tissues differing in β_1- and β_2-adrenoceptor density that "neuronal uptake removes noradrenaline in tissues with β_1- but not β_2-adrenoceptors". All these observations are in accordance with the concept of β_1-adrenoceptors being related to the neurotransmitter norepinephrine and β_2-adrenoceptors to the hormone epinephrine.

For the heart the situation is more complicated. One may have to differentiate here between the various aspects of heart action, such as the sino-atrial pacemaker, the conductive system, the heart muscle force etc. [58].

α_1- and α_2-adrenergic receptors

Parallel to the postulate for the β_1- and β_2-receptor differentiation outlined before, a similar postulate was presented by Ariëns and Simonis [9] for the α_1- and α_2-adrenergic receptors. Here, too, experimental evidence is growing.

The α-receptors in the rat aorta, which lacks functional sympathetic innervation [59], thus have an extrajunctional location; they are reported to be α_2-adrenergic in nature [6]. The α-receptors on platelets, which are extrajunctional anyway, are α_2-adrenergic in nature [60, 61]. Vascular effects of neuronally released norepinephrine are highly sensitive to prazosin, a selective α_1-adrenergic blocker, whereas those of exogenous norepinephrine are not. This, too, indicates a junctional location for the α_1- and an extrajunctional one for the prazosin-resistant α_2-receptors [62]. Yamaguchi and Kopin [63] conclude on the basis of a similar analysis that their results suggest that the pressure effects of exogenous catecholamine are predominantly mediated by α_2-receptors whereas the effects of sympathetic stimulation are the result of activation of α_1-receptors located in the vascular neuroeffector junctions. An analysis of the vascular effects of the ganglionic stimulant DMPP (1,1-dimethyl-4-phenylpiperazine) by means of selective adrenergic receptor blockers led Wilffert *et al.* [64, 65] to conclude: "The results can be explained by the presence of predominantly α_1- and β_1-adrenoceptors in the postganglionic sympathetic synapses and an extrasynaptic location of α_2- and β_2-adrenoceptors. The extrasynaptic receptors are possibly controlled by epinephrine from the adrenals."

The suggestions for further experimental testing of the hypothesis made with regard to the β_1- and β_2-receptors, such as studies by means of indirectly acting adrenergics, reuptake blockade, ganglionic sympathetic stimulation, and sympathetic denervation, hold true for the postulate on the α_1- and α_2-receptors as well.

As for β_1- and β_2-receptors, so also for α_1- and α_2-receptors occurrence in varying proportions in various tissues is likely, as demonstrated by Kobinger and Pichler [66].

Pre- and postsynaptic receptors

A classification of receptors on the basis of their location, such as junctional and extrajunctional, may pose problems. Epinephrine, for instance, serves as a hormone, acts extrajunctionally in mammals and, as indicated, as a junctional transmitter in amphibians [34, 35]. A classification on the basis of physiological responses is unattractive, too, since, on one receptor type a large variety of effects may be induced as exemplified by the responses induced on receptors for norepinephrine, epinephrine, histamine, acetylcholine etc. A particular problem arises with regard to the pre- and postsynaptic adrenergic receptors. There is good evidence for the existence of presynaptic α-receptors [3, 4], α_2-adrenergic in nature, on which the release of the neurotransmitter norepinephrine is inhibited, and presynaptic β_2-receptors on which this release is facilitated. On this point, Rand *et al.* [67] in their review on catecholamine receptors on nerve terminals conclude: "Thus it appears that the evidence is in favour of the prejunctional receptor being of the β_2-type." (See also Refs. 68–70.) As stated by Lands *et al.* [1], norepinephrine is a much weaker β_2-adrenoceptor agonist than epinephrine. With regard to the presynaptic α_2-adrenergic receptor, it turns out that the potency of epinephrine is 1.9×10^{-9} whereas that for norepinephrine is 1.2×10^{-8} [71]. Epinephrine appears to be the major stimulant for α_2-receptors in adipose tissue [72]. As indicated before, there undoubtedly is an overlap with regard to the action of epinephrine and norepinephrine on β_1-, β_2-, α_1- and α_2-receptors but epinephrine is more potent on the β_2- and α_2-receptors. In this regard the observation that circulating blood is rapidly cleared from norepinephrine by lung tissue, whereas epinephrine has a free pulmonary passage [73, 74], suggests that transmitter leaking into the circulation has only a secondary significance, in contrast to the hormone epinephrine. Although there is general agreement on the role of presynaptic α_2-adrenergic receptors in the inhibition of neurotransmitter (norepinephrine) release, the discussion whether here predominantly a feed-back inhibition by the neurotransmitter itself or whether catecholamines, predominantly epinephrine, reaching these α_2-recep-

tors from outside the junction are involved is still under discussion [75–77]. As an important aspect in this discussion one has to take into account that most of the conclusions on the role of the presynaptic α_2-receptors are based on effects obtained with norepinephrine, epinephrine and various types of blocking agents reaching the synapse via the circulation, i.e. by exogenous application. Whether exogenous norepinephrine, epinephrine or α_2-adrenergic blockers are capable of inhibiting or enhancing the release of neurotransmitter at presynaptic α_2-receptors does not matter from the physiological point of view. What matters is whether a back diffusion of neurotransmitter (norepinephrine) in the synaptic cleft or humoral catecholamine (particularly epinephrine) serves as a modulator of transmitter release [75–78]. The data presented indicate that the regulation of the release of neurotransmitter is possibly under the control of the neurotransmitter norepinephrine itself, but definitely also under the control of circulating catecholamines, particularly epinephrine (Fig. 1). Vascular and cardiac presynaptic β_2-receptors constitute a potential site for the antihypertensive action of β_1–β_2-adrenergic blocking agents such as propranolol [79].

The β_1- and α_1-adrenergic receptors seem to be exclusively postsynaptic in nature [61, 65]. The presynaptic (junctional) β_2- and α_2-receptors clearly match in their properties the 'humoral' extrajunctional β_2- and α_2-receptors. The occurrence of both postsynaptic α_1-receptors and humoral α_2-receptors on one and the same cell [80] implies a mixed population of α-receptors, such as observed also in certain venous smooth muscle and in arteriolar smooth muscle tissues.

On the basis of a detailed analysis of the role of α_1- and α_2-receptors, particularly in vascular smooth muscle, Langer and Shepperson [81] concluded: "Experimental evidence suggests that these two receptor populations may have different anatomical locations within vascular smooth muscle. . ., the α_1-subtype mediating responses to nerve stimulation, and the α_2- the responses to circulating catecholamines."

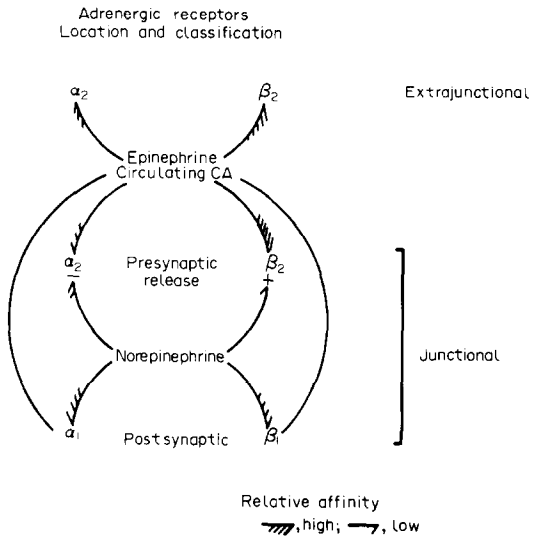

Fig. 1. Schematic representation of the relations between the neurotransmitter norepinephrine and the hormone epinephrine and the various, α_1-, α_2-, β_1- and β_2-adrenoceptors [89]. CA = catecholamine.

Non-junctional, humoral, adreno α_2-receptors may thus have an apparent postsynaptic localization. Experimental evidence indicates that in vascular smooth muscle the 'postsynaptic' α_1-adrenergic receptors lie predominantly within the synaptic cleft, whereas the α_2-receptors lie outside the cleft [80, 82–84]. It seems likely that, like the cholinergic receptors, the postsynaptic α_1- and β_1-adrenergic receptors are to be considered as involved in true transmission, that is a point-to-point transfer of information of one receptor–effector unit to another, while the humoral, α_2- and β_2-adrenergic receptors with their more general distribution would be involved in the modulation of the state of activity of more extended cell populations.

Receptor differentiation and denomination

One should be well aware of the fact that the differentiation between α_1-and α_2, and β_1- and β_2-adrenergic receptors is not parallel to the differentiation between, for instance, H_1-histamine and H_2-histamine receptors, which is much more analogous to the differentiation between α- and β-adrenergic receptors. On the other hand, the distinction between D_1- and D_2-dopamine receptors may well be related to a post- and presynaptic localization analogous to that outlined for the adrenergic receptors [85].

The concepts of α_1- and α_2-, and β_1- and β_2-adrenergic receptors were originally based on structure–action relationships [1, 2]. Taking into account the chemical relationship between the neurotransmitter norepinephrine and the hormone epinephrine, many of the adrenergic and adrenergic blocking agents used in the differentiation between postsynaptic neurotransmitter receptors and humoral receptors may be expected to show a certain overlap, and thus a non-selectivity in their action.

Various agonists such as acetylcholine, histamine, epinephrine, norepinephrine, dopamine, GABA etc. are small molecules relatively rich in polar groups. The corresponding competitively blocking agents, however, as a rule are composed of a relatively large hydrophobic (containing one or more aromatic rings) moiety and a smaller polar group. The hydrophobic moiety can impossibly bind on the highly polar receptor site, which in its chemical properties is complementary to the polar agonist. Competitive antagonists largely bind on accessory receptor areas which have a hydrophobic nature [9, 11]. Such areas are to be found at the interface of the receptor protein and the lipids of the membrane in which the receptor molecule is embedded. This implies that the binding site for the antagonist is largely determined by the qualities of the lipid anulus surrounding the receptor molecule. It is quite possible that the receptor–membrane interface for different tissues, i.e. different cell types, differs due to differences in the membrane composition. This makes comprehensible that, if compared on the basis of binding of antagonists, such receptors may mani-

fest themselves as being different, although they are identical as far as the receptor site for the natural messenger and the receptor–effector coupling is concerned. This may result in a further subclassification of the receptors which, although not of physiological significance, is definitely so from the pharmacological point of view.

In this relation the multiplicity of dopamine receptors up to D-4 and more reported [86, 87], predominantly based on the use of various 'selective' dopamine receptor blocking agents, may be mentioned.

One also has to take into account that the preparation of the receptor concentrates used in the various studies may influence the microenvironment of the receptors and thus add a further variable in this respect.

Criteria, agreed on by various researchers, for receptor differentiation as well as receptor denomination are badly needed, as is clearly exemplified by the incoherent plethora of dopamine receptors mentioned in the literature such as D_1, D_2, Di, De, DA_α, DA_β, Dai, Dae, Dai/e, DA_1, DA_2, D-1 and D-2 [88].

Conclusion

The postulate presented on the nature of the various adrenergic receptor types in mammalian tissues, namely postsynaptic α_1- and β_1-adrenergic receptors for preferentially the neurotransmitter norepinephrine and presynaptic and extrajunctional α_2- and β_2-adrenergic receptors for humoral, circulating, catecholamines, particularly the hormone epinephrine, has a good deal of internal logic. It supplies physiologists and clinicians with a physiological basis for the adrenergic receptor differentiation and therewith facilitates the interpretation of the actions of various types of adrenergic and adrenergic blocking drugs under physiological and pathological conditions. A good deal of experimental evidence converges in the postulate. This warrants its further investigation and evaluation.

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