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Reviews

Scaling of respiratory areas in relation to oxygen consumption of vertebrates*

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Summary. Resting oxygen consumption is generally related to the 0.75 power of the body mass. More recent studies on the morphometry of the lungs and gills of vertebrates indicate that the respiratory surfaces increase in area more closely to $M^{1.0}$. A possible explanation is that the gas exchange surface is more to be related to the *maximum* oxygen uptake capacity, rather than to the resting condition. However, recent studies, especially in African mammals, suggest that $\dot{V}_{O_2max}$ scales to a power similar to that for resting oxygen consumption and hence cannot be directly related to the respiratory surfaces.

In fishes the situation seems to be different as $\dot{V}_{O_2max}$ appears to increase more rapidly than standard $\dot{V}_{O_2}$. Consequently, the ratio between these two is greater in larger specimens and hence they have a greater scope for activity. A possible interpretation of this apparent difference may be related to differences in ventilation, as the tidal ventilation of lungs can lead to a reduction in the difference in oxygen pressure across the exchange surface, whereas in fish gills with increasing size and increasing water velocity there would be a reduction in the resistance to gas transfer. However, it is important to appreciate that such generalizations probably do not hold in all cases and the position of intermediate groups of vertebrates needs to be more closely assessed.

Study of changes in the structure and function of animals with increase in size has fascinated biologists for many years. It is not surprising when one remembers that man so often draws attention to other features of the universe in which studies are made of the largest, the smallest, the longest living or the earliest known etc. Extremes of body size clearly pinpoint some of the basic problems which are involved at intermediate levels but may also draw attention to new mechanisms (e.g. Weis-Fogh[55,56]). In the respiratory field studies of adaptations of man at the highest point in the world[16] or at the greatest depth to which he is able to dive in the ocean are further indications of this universal interest in extreme situations. The fact that gas exchange must take place through a limiting surface and that the oxygen absorbed is required for oxidative metabolism to provide energy for its body mass, i.e. proportional to volume, has directed interest to the surface/volume ratio. With increasing size, however, the proportion of the external surface involved in gas exchange is reduced and the oxygen requirement of different portions of the body volume also becomes non-uniform. Nevertheless, a broad relationship between surface and volume is apparent and is a valid guiding principle when making predictions. An expanding interest in comparative physiology and functional anatomy has now provided data on the relationships between body mass and various respiratory parameters which enable a more accurate assessment of this relationship.

The best known studies concern resting metabolism and body mass[7,20,37,57,58] for which oxygen consumption in unit time,

$\dot{V}_{O_2} = aM^b$

where b (the allometric or scaling constant) is approximately 0.75.

Although this is a valid generalization, many studies have shown that there are important variations in b depending on the species or group of animals concerned. The belief that this relationship is due to the heat conservation of warm-blooded animals gave rise to the so-called 'surface law'. However, a b value of 0.67–0.8 is not only found among warm-blooded animals and seems to represent other more general features of animals. Emphasis has tended to be given to studies at the interspecific level showing that values for the resting $\dot{V}_{O_2}$ of different species fall on the same straight line when plotted logarithmically against body mass. Studies at the intraspecific or intrageneric level tend to emphasise deviations from the more commonly found relationship. It has become increasingly apparent that it is important to consider or even expect such deviations not only in relation to resting metabolism but for other features of the structure and function of respiratory and circulatory systems. Even in the classical case of the 0.75 slope for resting metabolism in mammals, Heusner[21,22] has recently emphasized how 7 constituent species showing such a relationship each in fact has an interspecific slope of 0.67. It is evident that generalizations based upon too rigid an interpretation of overall intraspecific allometry must be viewed with scepticism. Theoretical considerations of changes in surface/volume ratio as a spherical organism increases in size assume a homogeneous utilization of the oxygen transferred[19]. With the evolution of diverse types of body organization such homogeneity has become greatly modified so that gas exchange becomes restricted mainly to the gills in aquatic organisms and the lungs of air-breathing vertebrates. In many forms, especially in the transition from an aquatic to a terrestrial mode of life, the skin also plays an important role[26,46]. Furthermore, the oxygen uptake of different organs can vary from such highly active organs as the brain, heart and liver to fat and bony structures where the weight specific $\dot{V}_{O_2}$ is very much less. Nevertheless, the whole organism must conform to certain limitations related to its overall size which determine, for example, the volume of blood which must be transported to different distances, the amount of tonic activity in muscles and other supportive elements and the size of the absorptive areas for food and gas exchange. The sum of the individual metabolic requirements of these parts of the organism constitutes the overall resting metabolism, but such balance sheets are available for very few animals[35,36]. Metabolic activity is commonly assessed by measuring $\dot{V}_{O_2}$ but this may give an underestimate if the animal is deriving much of its energy requirements from anaerobic processes, many of which have been shown to be far more widespread among vertebrates than was supposed a relatively short time ago[2,24].

Scaling of respiratory surfaces

Increasing attention has been paid to measurements of the area of the gas exchange surfaces, especially for mammals and fish. Such measurements are fraught with difficulties and are very laborious but modern techniques have improved their accuracy and speed[27,30,52,53]. The gill or lung surface forms a significant multiple of the external body surface which increases with size at a rate which is not always directly proportional to body mass and often to a power function of about 0.8. Once again, however, studies based upon individual species have shown a wide range of values, e.g. the gill area of different species of fish ranges from 0.5 to 1.0[27,29,34]. Considerations of the surface/volume ratio of a hypothetical spherical organism have usually supposed a direct correlation between the surface and resting metabolism and it might, therefore, be supposed that the relationships of both $\dot{V}_{O_2}$ and respiratory area would have the same mass exponent (b). Again, a generalization of this kind would seem to have some validity when considered over the whole range of body sizes but such a simple relationship is not always found for individual species or groups of closely related species. Such generalizations also assume that the comparison is made between organisms of comparable construction and shape. Changes in allometric constant are well known to occur during evolution[8,29].

Measurement of active oxygen consumption

One of the main reasons for increased study of gas exchange surfaces has been a renewed interest during the last 20 years in the comparative respiratory physiology of different vertebrates[25,28,43].

Measurements of $\dot{V}_{O_2}$ have formed an important part of this work and it has become essential to define the experimental conditions.

Activity is a most important factor and this period has been characterized by the development of apparatus for maintaining animals at different speeds of locomotion. The treadmill of mammalian exercise physiologists has been adapted for use with animals ranging from lizards to kangaroos[9,41,47]. Water and air tunnels also enable data to be obtained during aquatic and aerial locomotion[4,5,48]. Most relationships to body mass mentioned above refer to resting or basal metabolism. However, in many species the definition of this condition is not easy; one commonly used method (fig. 1) being to extrapolate the relationship between $\dot{V}_{O_2}$ and speed of locomotion to zero speed[12,50,51]. In most cases the values obtained for this standard $\dot{V}_{O_2}$ are comparable to those obtained where the same species is kept quietly in a respirometer in order to reduce activity. There are, of course, many levels of active metabolism[13] and for comparisons it is of interest to know the maximum oxygen uptake at a speed of locomotion which can be defined with respect to duration and velocity and above which the animal depends on anaerobic sources for its energy and hence the O_2 uptake levels off. Values obtained under conditions of this nature are usually referred to as the maximum oxygen consumption ($\dot{V}_{O_2max}$). In some cases it is difficult to be sure that the values are truly maximal. Study of $\dot{V}_{O_2}$ is especially relevant in relation to possible limitations due to the extent and nature of surfaces for gas exchange and it is only relatively recently that a range of values has been obtained. In a number of organisms the relationship between resting and active $\dot{V}_{O_2}$ is regarded as an indication of the 'scope for activity'[13]

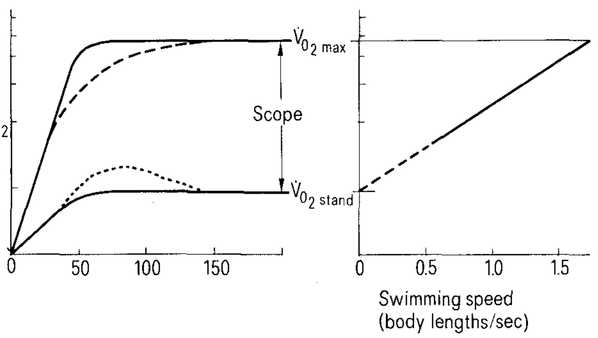

Figure 1. Diagram illustrating the relationship between standard oxygen consumption, maximum oxygen consumption and P_{O_2} in the external environment. The relationship between the standard oxygen consumption and the maximum oxygen consumption in relation to swimming speed is also illustrated. The difference between $\dot{V}_{O_2max}$ and $\dot{V}_{O_2stand}$ is the so-called 'aerobic scope for activity'.

and indicates the extent to which an animal can raise its activity from resting to its most active level, (fig. 1). Another way of expressing this relationship is the 'coefficient of expansibility'[10] which indicates the factor by which standard $\dot V_{O_2}$ can be increased during maximal activity. A value of 5–10 seems generally applicable and increases with body mass, at least in most of the species indicated in figure 2. Lines drawn in this figure are based upon differences between 2 regression lines that have been established for these particular species. For birds it has also been concluded[42] that the ratio of active to standard metabolism increases with body mass.

However, there are other observations in the literature which indicate little change with body size and these include recent measurements on African mammals[54]. The relatively slight increase in tortoises and turtles may be related to difficulties in obtaining maximum activity in these organisms and is a problem for all reptiles[3]. The great increase with size in the two fishes shown here is quite remarkable but again there are species where this does not seem to occur, e.g. some air-breathing species such as *Channa punctata*.

In addition to studies of different levels of oxygen consumption there has also been an interest in the relationship between these measurements and the body size of different groups of animals which enables them to be incorporated in allometric comparisons between species (table).

Scaling of respiratory surfaces in relation to $\dot V_{O_{2stand}}$ *and* $\dot V_{O_{2max}}$

Theoretically it is possible to envisage several relationships between the scaling of different features of the respiratory mechanism which have been discussed, i.e. respiratory area, diffusing capacity for oxygen, resting $\dot V_{O_2}$, active $\dot V_{O_2}$, scope for activity. Some of these are indicated by 6 diagrams in figure 3. In (a) and (b) the regression lines for standard and active $\dot V_{O_2}$ are parallel; in (a) the surface area or diffusing capacity increases with body size more rapidly than does $\dot V_{O_2}$ whereas the opposite is shown in (b). In (c) and (d) the exchange surface capability increases at the same rate as active $\dot V_{O_2}$ but in (c) standard $\dot V_{O_2}$ increases less rapidly whereas in (d) the slope of the regression line for standard $\dot V_{O_2}$ is steeper than for active $\dot V_{O_2}$ and surface area. The last 2 possibilities show examples in which the area or diffusing capacity increases with body mass at the same rate as does resting (standard) $\dot V_{O_2}$. In (e) active $\dot V_{O_2}$ increases more rapidly than the other two lines whereas in (f) it has a less steep slope. The obvious possibility in which all three are independent has not been represented.

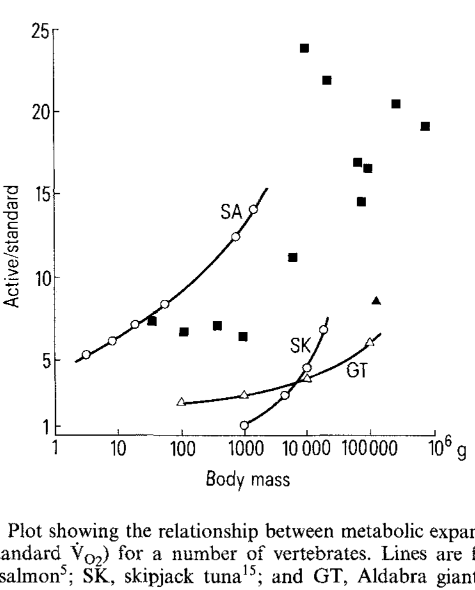

Figure 2. Plot showing the relationship between metabolic expansibility (active/standard $\dot V_{O_2}$) for a number of vertebrates. Lines are for SA, sockeye salmon[5]; SK, skipjack tuna[15]; and GT, Aldabra giant tortoises[33] and are based on differences between two regression relationships. Individual points for a variety of mammals (■) are taken from Pasquis et al.[41] and for a sea turtle from Prange and Jackson[44].

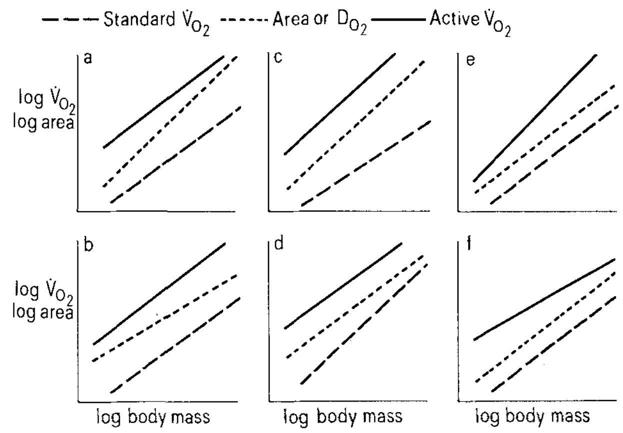

Figure 3. Hypothetical diagrams showing relationship to body mass of $\dot V_{O_{2stand}}$ $\dot V_{O_{2active}}$ and also the area of the gas exchange surface or better, but not always available, the morphometric diffusing capacity (D_{L,O_2}). In (a) and (b) both $\dot V_{O_2}$ lines have the same slope whereas that for the respiratory surface increases either more rapidly (a) or less rapidly (b) with body size. In (c) and (d) the $\dot V_{O_2}$ active and respiratory surface lines are parallel, whereas $\dot V_{O_{2stand}}$ decreases more or less rapidly than both of them. In (e) and (f) respiratory surface and $\dot V_{O_{2stand}}$ are parallel whereas the $\dot V_{O_{2active}}$ increases more (e) or less rapidly than either of them with increasing sizes. For further description see text.

Associated with these different theoretical possibilities are different ways of considering the extent to which the properties of the gas exchange surfaces may limit the oxygen uptake and activity of different vertebrates. During comparative studies several of these theoretical possibilities have been observed (fig. 4). In some early studies of gill area[40] it was found that the surface increased by approximately the same power as the value regarded as typical for the resting metabolism of fishes, i.e. 0.82 (Winberg[57]). More detailed studies of other species, however, revealed that this situation was exceptional as in several species gill area increased more rapidly than standard $\dot V_{O_2}$ (fig. 4a). It was hypothesized[27] that the whole of the gill surface was not normally involved in gas exchange during resting metabolism and that this proportion would increase during more active swimming and perhaps it was more appropriate to regard the slope of the gill area line as representing the relationship between active $\dot V_{O_2}$ and body mass. In such circumstances, $\dot V_{O_2}$ for active metabolism would diverge from that for standard metabolism with an increase in size and consequently larger fish would have a greater scope for activity. Confirmation of this theoretical deduction was available in the literature for the only fish species (salmon) which had been investigated in any detail from this point of view[5, 6].

The results recently obtained by a thorough study of maximum oxygen consumption and its relationship to standard $\dot{V}_{O_2}$ for mammals[54] are in agreement with an earlier study on a single genus *(Lacerta)* of lizard[9] in which the slope (0.75) relating maximum $\dot{V}_{O_2}$ to body mass was the same as that for standard $\dot{V}_{O_2}$ (fig. 4b). Furthermore, in *Lacerta* a matching of the scaling for maximum $\dot{V}_{O_2}$ with D_{L,O_2} was also found. In this latter aspect there is, however, a significant difference from the results obtained for the mammalian lung where D_{L,O_2} was proportional to $M^{1.0}$ (14). Among other reptiles it has been found that the scaling of active $\dot{V}_{O_2}$ has a steeper slope (0.97) than that of standard $\dot{V}_{O_2}$ (0.83) but data is not available for lung morphometry[33]. In this latter case, then, with increase in size there is greater scope for activity (fig. 4c) and it has been suggested that this might have significance in the life of the giant tortoises of Aldabra[33]. A similar increase in metabolic scope has been found for other chelonians[44].

Against this background, earlier results and hypothesis put forward in relation to scaling of fish respiratory surfaces and oxygen consumption are of interest. Originally measurements of the surface area and similarly diffusing capacity were thought to scale (0.85) very close to those of resting $\dot{V}_{O_2}$[40]. Further studies revealed, however, that this similarity for tunas was not found in other fishes where both gill area and standard oxygen consumption increased with body weight to exponents between 0.5 and 1.0. Furthermore, for many individual species the scaling of gill surface area and resting $\dot{V}_{O_2}$ were not the same. From this and other investigations it became apparent that the entire gill surface is not utilized under resting conditions because it is under-ventilated or underperfused. It was suggested, therefore, that measurements of gill surface area were more likely to be related to *maximum* $\dot{V}_{O_2}$ than to standard $\dot{V}_{O_2}$. Hence in species where there is a difference in slope of the $\dot{V}_{O_2\text{stand}}$ and gill area plots would suggest a difference in slope for the standard and maximum $\dot{V}_{O_2}$ relationships. Unfortunately, very few measurements have been made of maximum oxygen consumption of fish over a range of body sizes. One example is well documented – the salmon by Brett[5] and Brett and Glass[6] who found a divergence between the regression lines for active and standard metabolism. This direct finding of an increase in metabolic scope with increase in body mass is of the same type as that deduced independently for the rainbow trout[27] from measurements of gill area and of standard $\dot{V}_{O_2}$. In the latter case gill area scales as $M^{0.932}$ whereas standard $\dot{V}_{O_2}$ is proportional to $M^{0.8}$. Some recent studies on tunas[15] have shown that the slope for active metabolism is greater than 1.0 whilst for $\dot{V}_{O_2\text{stand}}$ it is about 0.75 and gill area scales as $M^{0.85}$ (table). It would seem that in skipjack these 3 features of the respiratory function scale independently of one another. The wide confidence limits indicate that they may not be so different, but it would appear that there is an increase in O_2 transfer/unit gill surface with an increase in body mass.

It may be concluded that some of the data available for lower vertebrates supports the view recently emphasized by Heusner[22] that the coupling between respiratory structure (area and D_{L,O_2}) and function may not be so close as Weibel and Taylor suppose. However, it is also important to give more detailed consideration to the precise nature of ventilation and perfusion of the surfaces as any scaling of these processes will affect the overall relationship.

Comparison between mammalian and fish ventilation

Thus on the present evidence it seems that the situation in fish may be different from that found in mammals by

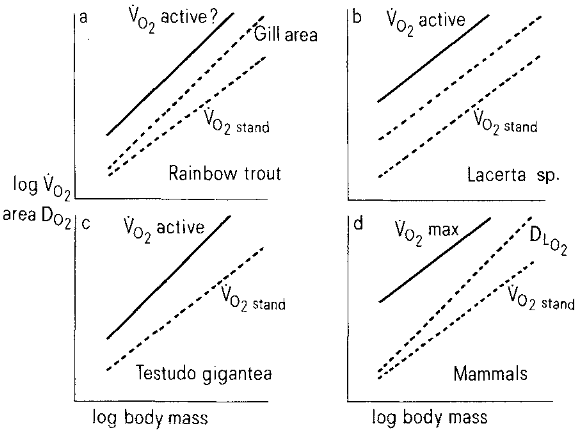

Figure 4. Diagrams illustrating slopes of the bilogarithmic plots for body mass against active or maximum oxygen consumption, standard oxygen consumption and respiratory surface for 4 examples from the literature. In (a) the relationships suggest parallelism between the lines for active $\dot{V}_{O_2}$ and gill area in the rainbow trout whereas the standard oxygen consumption has a lesser slope[27]. For some lizard species (b) the 3 lines have the same approximate slope[9]. In (c) the lines for active and standard oxygen consumption of a giant tortoise diverge[33]. In (d) the $\dot{V}_{O_2}$ lines have the same slope whereas the diffusing capacity of the lung increases more rapidly than either of them in this example based upon African mammals[54].

Allometric coefficient (b) for the standard and active oxygen consumption of a variety of vertebrates. Where available the corresponding coefficients for surface area of the respiratory organ or the oxygen diffusing capacity is also listed

	Resting, standard or or minimal $\dot{V}_{O_2}$	Surface area of respiratory organ	O_2 diffusing capacity of respiratory surface	Active $\dot{V}_{O_2}$ or $\dot{V}_{O_2\text{max}}$
Mammals	0.75 (37)			
All species	0.734 (7)	0.95 (14)	0.99 (14)	0.73–0.79 (41)
African (21sp)		1.188 (14)	1.265 (14)	0.769 (47)
Birds		0.881 (39)	0.888 (39)	1.0–1.17 (42)
Passerine	0.724 (38)		1.02	
Non-passerine	0.723 (38)		0.864	
Lacerta sp.	0.756 (9)	0.69 (9)	0.69 (9)	0.747 (9)
Green turtle	0.826 (44)			0.944 (44)
Giant tortoise	0.821 (33)			0.969 (33)
Salamanders	0.65 (49)		0.54 (49)	
Flounder (adult)	0.812 (11)	0.82 (32)		
Salmonid (rainbow trout and Pacific salmon)	0.80	0.932 (31)	0.9	0.97 (5)
Skipjack tuna	0.56 (15)	0.85 (40)		1.19 (15)
Channa punctata		0.6225 (17)	0.6299 (17)	0.6249 (18)

recent investigations[54]. One must beware, however, of making generalizations for all fish and certainly not for all cold-blooded vertebrates for there are differences among reptiles. It is possible, however, to envisage reasons for differences between fish and mammalian systems because of the fundamentally different nature of gill and lung ventilation. In fish the flow of water across the respiratory surface is more or less continuous and uni-directional and contrasts with tidal ventilation and its inherent dead space within the terminal airways. This difference may be particularly important as it is this latter aspect which Weibel and Taylor[54] have suggested as a possible reason for a difference in the scaling of $\dot{V}_{O_2max}$ and D_{L,O_2}. In particular they suggest a possible reduction in alveolar P_{O_2} with size and consequently a reduced ΔP_{O_2} which provides the driving force for O_2 transfer across the air/blood barrier. In contrast, a dimensional analysis of the fish gill system[23,29] has indicated that during increase in size of resting bass[45] and trout there would only be a slight increase in water velocity between the secondary lamellae and that the water film would make an almost constant contribution to the resistance to O_2 transfer/unit area. Thus as the fish grows the gill system increases in total size more by an increase in the total number of pores, each maintaining more or less constant dimensions, rather than by changes in the dimensions of individual inter-lamellar spaces. Furthermore, with increase in size there would be an increase in swimming speed (α body length[1]) and in those fish where ventilation is aided by their forward movement this would serve to further improve ventilation and reduce any dead space. It would seem, therefore, that in fish many factors would tend to prevent a fall in ΔP_{O_2} between the water and the blood with an increase in body size. On the contrary with the increased ram ventilation of larger fish there will probably be a decrease in thickness of the water film and hence a reduction in the effective water/blood barrier which would help maintain ΔP_{O_2} with a consequent increase in the oxygen transferred/unit area.

During an earlier discussion of these relationships[27] it was concluded that with an increase in size, either $\Delta P_{O_2}/t$ (t = barrier thickness) must decrease or $\dot{V}_{O_2max}$ must increase more rapidly than $\dot{V}_{O_2stand}$. It now seems possible that the first alternative is found in mammals whereas the second is more typical of fishes. Some caution is necessary, however, as there is also data in the literature to suggest that there are other possibilities in both groups.

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Recent advances in the use of selective neuron-destroying agents for neurobiological research

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During the last few years, the use of selective neuron-destroying agents has become one of the most widely used approaches in neurobiological research. The general aim of investigators using neuron-destroying agents is to provoke a more or less extended, but anatomically verifiable, neuronal degeneration and to study the consequences of the lesion from anatomical and/or functional points of view. Neuron-destroying agents are powerful tools to investigate many basic aspects of brain organization but, at the same time, they give rise to several problems related to the mechanism of action of the drugs used and to possible drawbacks in the interpretation of the results.

The aim of the present paper is to present some of the more important findings obtained, in recent years, from the experimental use of neuron-destroying agents and to make, whenever possible, a critical appraisal of the potential usefulness and drawbacks for each compound. Our attention will be primarily focussed on agents producing degeneration of nerve cell bodies; we will not make any attempt to review the extensive literature concerning the action of drugs having a primary neurotoxic action towards chemically-characterized nerve endings, such as 6-hydroxydopamine, 6-hydroxydopa, 5,6-and 5,7-dihydroxytryptamine[2,57,65,66,80,99,112,131,132,155].

Kainic acid

Since the discovery of the neuroexcitatory[60,144] and neurotoxic[23,54,110] action of kainic acid on invertebrate and vertebrate neurons, this drug of algal origin has been extensively used in experimental neurobiology. In the present paper we will not consider in detail the bulk of earlier findings, adequately reviewed in previous publications[20,87]; we will rather focus our attention on those aspects which are more relevant to the problem of the