Platelet and Brain Fatty acid transfer: Hypothesis on Arachidonic Acid and its relationship to Major Depression

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Abstract

Depression may be linked to changes of the fatty acid profile in many biological districts such as platelets, plasma phospholipids, rat brain and red blood cells.
The platelet is one of the most extensively researched biological markers in psychiatry. In an animal model of depression, the high level of arachidonic acid, found in the brain, in platelets and in other biological material indicates a possible relationship between platelets and brain. For this purpose we investigated platelet fatty acid composition in humans (vein and artery) and in pigs (vein and brain). The findings are consistent with the hypothesis, in the case of Arachidonic Acid, of a specific link between the two districts (platelets and brain) and of the existence of particular conditions which can cause a dangerous accumulation of Arachidonic Acid within the brain.

Introduction

Recent studies have demonstrated the existence of significant differences of fatty acids composition of the cell membranes of platelets between depressed humans and apparently healthy subjects. (Cocchi M. et al. 2008, 2009). These differences were identified through the use of advanced mathematical tools. In particular an Artificial Neural Network (ANN), the Self Organizing Map (SOM) described by Kohonen (1982) was employed. The SOM isolated three fatty acids: Arachidonic Acid (AA), Linoleic Acid (LA) and Palmitic Acid (PA), and was able to map the two different populations (normal and depressive) recognizing as similar the subjects belonging to the same population. The platelet is one of the most extensively researched biological markers in psychiatry (Camacho and Dimsdale, 2000; Plein. and Berk, 2001; Musselman et al. 1996). Arachidonic Acid, in particular, seems to be deeply involved, as biochemical marker, in depressive disorder (Tiemeier et al. 2003; Green et al. 2005; Cocchi et al. 2008, 2009). Because depression is a brain disorder we assumed that Arachidonic Acid could be involved in both, brain and platelets, and that a possible link between the two districts was possible.

All the ANNs tested gave essentially the same result. However, one type of ANN, known as a self-organizing map (SOM) (Kohonen T. 1982), gave superior information by allowing the results to be described in a two-dimensional plane with potentially informative border areas. A series of repeated and independent SOM simulations, with the input parameters being changed each time, led to the finding that the best discriminant map was that obtained by inclusion of the following three fatty acids: linoleic acid (C18:2 n-6), arachidonic acid (C20:4 n-6) and palmitic acid (C16:0). The Arachidonic Acid values were used to study the transfer hypothesis between brain and platelets.

Methods and Materials

For the purpose of the study we collected the data obtained from pig brains and platelets, and from the platelets of healthy human's (vein) and from the platelets (vein and artery) of subjects with ischemic cardiovascular disease (pathology with high affinity with depression). (Cocchi et al. 2008, 2009; Licinio et al. 2002)
Platelets and brain fatty acids were analyzed according to Passi et al. (2003) and Iida et al. (1991)
Statistical analyses were carried out using the STATISTICA version 7 data analysis program (StatSoft Inc., Tulsa, OK, USA; http://www.statsoft.com/ webside).
The concentrations of those fatty acids surviving the one-

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way ANOVA were entered, blind to group status, age or gender, into a wide variety of different types of ANN. These were run on a PC on a C/C++ platform. The results from the different ANNs were compared.

The study was carried out according to the Declaration of Helsinki. The subjects were given details of the study and they gave their informed consent. The study was approved by the local research ethics committee.

Results

WORK 1: Correlations between fatty acids in the brain and in the pig's platelets.

In order to determine any links existing between the fatty acid composition (FA) of the platelets and the brain we have evaluated the entire FA pattern in both the districts of 26 pigs. We proceeded with the determination of all the correlations (according to Pearson) between the brain and platelet fatty acids. Some correlations were found to be significant (p < .05) and are highlighted in Table 1.

The linoleic and oleic acids in platelets are negatively

Correlations (Brain and Platelet in PIG) Sig. level p < .05000 N=26						
	Platelet C16:0	Platelet C18:0	Platelet C18:1 n9	Platelet C18:2 n6	Platelet C18:3 n3	Platelet C20:4
Brain C16:0	-.1039	-.1913	.2005	.1930	.0938	.1772
	p=.613	p=.349	p=.326	p=.345	p=.648	p=.387
Brain C18:2n6	-.3295	.2064	-.0806	.0542	.2889	-.2597
	p=.100	p=.312	p=.695	p=.793	p=.152	p=.200
Brain C22:0	.3560	.3092	-.5149	-.4811		
	p=.074	p=.124	p=.007	p=.013		
Brain C20:4n6	-.0169	-.1402	.1661	.0279	.0032	.1649
	p=.935	p=.495	p=.417	p=.892	p=.988	p=.421
Brain C24:0	.3267	.0277	-.0182	-.0194	-.0576	-.2518
	p=.103	p=.893	p=.930	p=.925	p=.780	p=.215
Brain C24:1	.4739	-.3974			.2299	.1494
	p=.014	p=.044			p=.259	p=.466
Brain C22:6n3	-.0269	.0416	.0998	-.0870	.2263	.0744
	p=.896	p=.840	p=.628	p=.673	p=.266	p=.718

Table 1 - Correlations between some fatty acids in the pig's brain and platelets. Those which are significant are highlighted (in dark).

correlated with the beenic acid of the brain; palmitic acid of platelets (with positive correlation) and stearic acid (with negative correlation) are correlated with the nervonic acid of the brain.

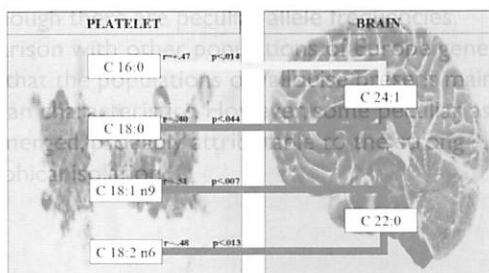The results have been schematised as reported below in Fig. 1.

Fig. 1 - Chart of the significant correlations between platelets and brain. In the chart set up, the 4 significant correlations identified are highlighted with a line. The dark line indicates a negative correlation (r < 0) while the light grey a positive correlation (r > 0).

WORK 2. Correlations between the fatty acids in the pig's brain.

We evaluated the FA pattern in the brains of 39 pigs and looked for any possible correlation between the different FA, in order to evaluate any relations inside the brain. In particular, first of all there was an evident correlation of arachidonic acid (C20:4) with beenic acid and nervonic acid. The first result observed is a positive correlation between arachidonic and nervonic acids.

The values measured are reported in Table 2 below and are schematised in Fig. 2.

	Corr.
	C20:4n6
BRAIN	
C22:0	-.1234
	p=.454
C24:1	.4036
	p=.011

Table 2 - Correlations between Arachidonic Acid and Beenic Acid and Nervonic Acid. There is a significant correlation between Arachidonic and Nervonic fatty acids.
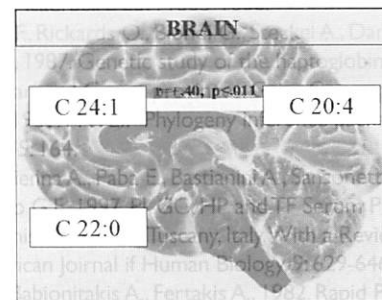

Fig. 2 - Chart portraying the correlations of some FA in the pig's brain. The light grey line represents the positive significant correlation that links the Arachidonic Acid to the Nervonic Acid, in the brain

The results illustrated relating to Work 1, together with those described above relating to Work 2, can be put together and schematised as is reported in the following Fig. 3.
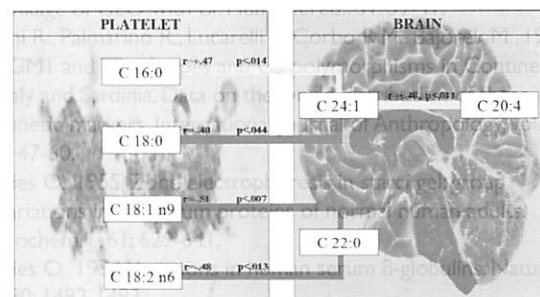

Fig. 3 - Chart of the correlations between pig platelets and brain. The chain of correlations shows how the Palmitic acid and Stearic acid of the platelets are linked with the brain Arachidonic acid.

The chart reported in Fig.3 highlights the correlation between the concentration of two fatty acids of the platelets (Palmitic and Stearic) and the brain Arachidonic acid level.

Bearing in mind the fact that there are many reports in the

literature highlighting the undoubted link between depressive disease and the levels of Serotonin in brain and platelets (Kim et al., 1982; Green et al., 2005), in turn, linked to the levels of arachidonic acid of the same district, it is possible to consider a continuous chain of relations. In other words, if we do not ignore the fact that there is a chain of correlations that links the levels of some platelets FA (in particular, Palmitic and Stearic acid) to those of the brain Arachidonic acid, a model that links platelets to depression can be assumed, and Depression-Serotonin-Arachidonic Acid relations are reported in the literature. Work 1 and Work 2 show a link between Arachidonic Acid and Platelets, the missing link that completes the chain between platelets and depression.

The evaluation of the correlations relating to arachidonic acid offers another clue. In fact, if we examine the statistical significances between arachidonic acid and its precursors, no significant correlation can be observed, as reported in Table 3.

Fig. 4 - Fatty acids in the human pla- telets: in dark grey, the negative corre-lations, in light grey the positive ones.

the human being, as a precaution we have, nonetheless, constructed and considered a model of a qualitative and not quantitative type. The result obtained by the combination of three works is illustrated in Figure 5.

	PIG N=39 Brain	
	C20:4n6
Correlatio	
C18:2n6	-.172
	p=.295
C18:3n6	NOT PRESENT
C20:3n6	.2313
	p=.157

Table 3 - Significance of the correlations between arachidonic acid and its precrsors. No statistical significance was measured

Therefore the arachidonic acid present in the brain does not appear to be produced by the brain itself. This statement is confirmed by the modern international literature. (De Mar, 2006)

WORK 3. Correlations among fatty acids in human platelets. The correlations between all of the platelet fatty acids of sixty supposedly healthy people were evaluated. Some correlations are reported in Table 4, where the statistically significant ones are evidenced ($p < 0.05$). The significant correlations have been schematised using the convention of associating dark grey with r negative values and light grey with the r positives (Fig. 4).

Fig. 5 - Chart of the links between vein and brain, in terms of fatty acids, according to what was found in Work 1, Work 2 and Work 3.

The key point that needs to be focussed on is that, through a chain of relations, the platelet levels of arachidonic acid are connected with those of the same acid in the brain. This is, above all, a confirmation of the result obtained by the SOM ADAM study that identifies arachidonic acid as an important biomarker of the depressive disorder (Cocchi et al., 2008, 2009). For a more careful qualitative analysis of the link between the levels of arachidonic acid in the platelets and in the brain, we should consider the signs of the correlations (the r value of positive or negative Pearson).

Observing Fig. 5, we start from the arachidonic acid in the platelet and consider, for instance, a hypothetic increase. According to the proposed model, this is matched by a decrease in the palmitic acid, again in the vein. Following on from this, if we associate the increase in the nervonic acid in the brain, it is, in turn, correlated with a decrease in arachidonic acid, again in the brain. Analogously, by taking the alternative path, from the arachidonic acid in the platelet, by assessing its correlation with the linoleic acid and then the oleic acid with the stearic acid, in turn connected with the nervonic in the brain, ending once again with the arachidonic acid in the brain, we get the same result: an increase in arachidonic acid in the platelet (vein) is matched by a decrease of the same acid in the brain. In brief, with an analogous argument it can be seen that, vice-versa, a decrease in the vein is matched by an increase in the brain. Having already observed that the

Correlations N=60					
	C16:0	C18:0	C18:1	C18:2	C20:4
C16:0	1.0000	-.2458	.4225	-.3609	-.2822
	p= —	p=.058	p=.001	p=.005	p=.029
C18:0	-.2458	1.0000	-.4414	-.3566	.0880
	p=.058	p= —	p=.000	0	p=.504
C18:1	.4225	-.4414	1.0000	-.2545	-.3015
	p=.001	p=.000	p= —	p=.050	p=.019
C18:2	-.3609	-.3566	-.2545	1.0000	-.3216
	p=.005	p=.005	p=.050	p= —	p=.012
C20:4	-.2822	.0880	-.3015	-.3216	1.0000
	p=.029	p=.504	p=.019	p=.012	p= —

Table 4. Some correlations between the AG of the platelets in humans. The statistically significant correlations are in dark grey.

Bearing in mind that Work 3 regards humans whereas Work 1 and Work 2 deal with the pig, although it is recognized that the pig is an excellent biological model for
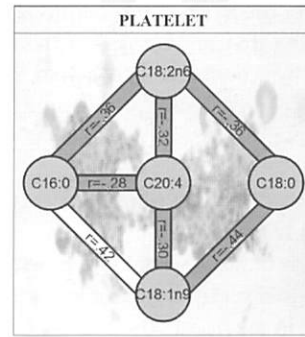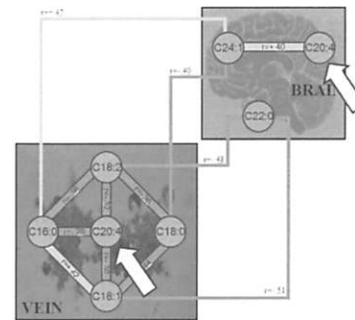
arachidonic acid in the brain is not produced by the brain itself, and observing that, an increase in the fatty acid in the brain is matched by a decrease in the vein, is it plausible to think that the platelets are one of the vehicles that actually transport it to the brain?

WORK 4. Vein and artery platelets fatty acid composition in humans.

The whole pattern of fatty acids in 50 humans (with a history of ischemic disease) was studied both in the vein and in the artery. In particular, the trend of arachidonic acid was studied, introducing also the parameter:

$\varnothing C20:4 = C20:4$ Vein $- C20:4$ Artery

It expresses the variation in arachidonic acid between vein and artery. If there are differences in the levels in the vein and artery, the $\varnothing C20:4$ quantify the entity and the specific direction of the variation. The correlations in the above-cited parameters were assessed and the following results were obtained:

C20:4 Vein and C20:4 artery expressed an $r = 0.82$, $p < 0.00000$;

C20:4 Vein and $\varnothing C20:4$ expressed an $r = 0.52$, $p < 0.00012$.

It can be considered that a possible decrease of arachidonic acid in the artery is associated with a drop of the same fatty acid in the vein, in turn, correlated with a decrease of the $\varnothing C20:4$. This mean an increase of $-\varnothing C20:4$ of arachidonic acid output from the venous-artery circuit. In other words, a diminution of arachidonic acid in the artery corresponds to a diminution in the vein and an increase of the exit "towards the outside" of the same acid. Combining the result just described with Work 1, Work 2, and Work 3 and reporting only the relevant part, we obtine the chart in Fig. 6.
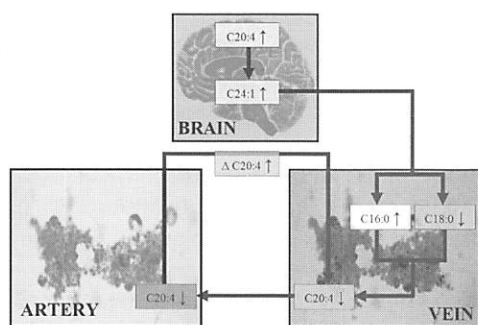

Fig. 6 - *Chart of the union of Work 1, Work 2, Work 3 and Work 4. Arachidonic acid in vein, artery and brain. An increase in arachidonic acid in the brain is associated with a chain of correlations, an increase in the exiting flow between artery and vein of the same acid.*

From Figure 6 we try to hypothesise an increase of the arachidonic acid in the brain. This is correlated with an increase in nervonic acid in the same district and there is also, respectevly, a correlation with an increase of the palmitic acid and a decrease of the stearic acid in the vein. Also in the vein, a decrease in arachidonic acid is correlated with this dynamic and in turn correlated with a decrease in the artery and an increase in the outgoing flow from the venous-artery circuit. More simply, an increase in

the arachidonic acid in the brain is associated with an increase in its outgoing flow from the venous artery circuit. Naturally, the argument is analogous, if we consider a decrease of the arachidonic acid in the brain, the decrese is associated with an increase of the same acid in the venous artery circuit and a further increase in its flow entering the system.

This result does not have the presumption of stating that all the arachidonic acid present in the brain is brought by the platelets alone or that the platelets are the only vehicle transporting the arachidonic to the brain. It is just that the results achieved lead us to think that the platelets are one of the vehicles transporting the arachidonic acid to the brain according to what has been schematised in Fig. 7.
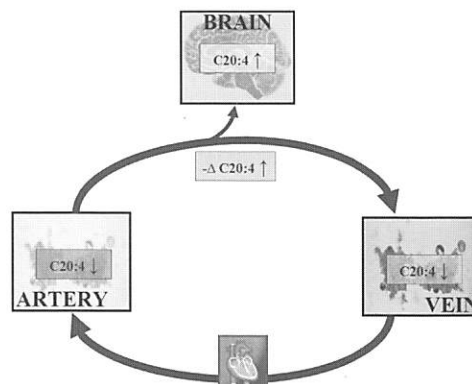

Fig. 7 - *Transport's chart of arachidonic acid hypothesized, in agreement with the results obtained. An increase in the arachidonic acid in the brain is compatible with a decrease in the venous-artery; the reasoning would be analogous (and with opposite results) if we hypothesise a decrease in the arachidonic acid in the brain, which is associated with a venous-artery increase.*

Reflections, considerations and hypotheses

It has been observed that there is a statistically significant correlation ($r = 0.52$; $p < 0.00012$) between arachidonic acid in the vein and the parameter $\varnothing C20:4$. This suggests constructing a simple linear regression in order to study the dynamic in detail (Fig. 8).
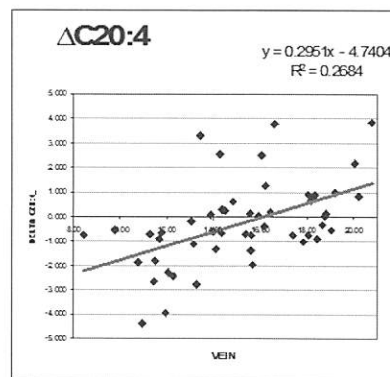

Fig. 8 - *curve of the linear regression between venous platelet C20:4 and the $\varnothing C20:4$. The graph shows in the x-axis the C20:4 in vein, in the y-axis the $\varnothing C20:4$. The regression curve is in dark.*

If we focus our attention on the regression line we can recognise the dynamics of the arachidonic acid already

described. Starting from the intersection point between the regression line and the x axis (the axis Vein C20:4) and shifting towards the right, there is an increase in arachidonic acid in the vein, which is matched by an increase in flow between brain and vein, with the consequent decrease of the same fatty acid in the brain. The situation is the opposite if we move leftwards along the x axis. In order to obtain a more detailed vision of the mean trend we have constructed a polynomial regression of the fourth degree. The curve obtained is reported in Fig. 9, 10.
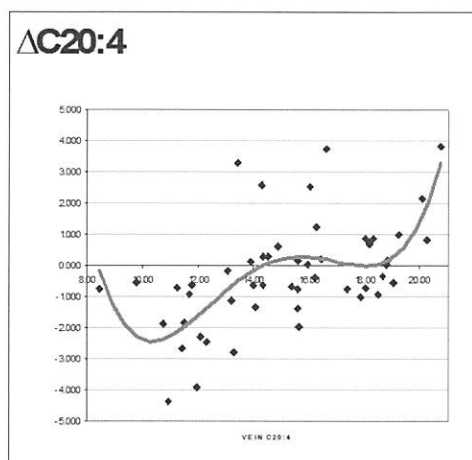

Fig. 9 - *Polynomial regression of the 4th degree relating to the values of C20:4 in the vein (x-axis) versus those of ∅C20:4 (y-axis).*
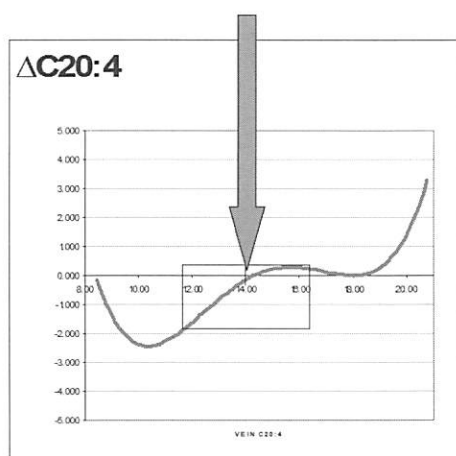

Fig. 10 - *Overlap of the mean values of arachidonic acid in 'normal' subjects, on the polynomial regression curve. The arrow indicates the mean value and the box the standard deviation of the above-cited 'normal' subjects*

A careful analysis of this regression curve suggests some very interesting considerations.
If we consider the mean value of the arachidonic acid relating to subjects with no depressive or cardiac diseases, evaluated in previous trials (Cocchi *et al.*, 2008), it reaches a value (as % of total fatty acids) of 14.06±2.40 (mean±SD).

Overlapping this value on the regression curve just introduced, we can observe that the mean value of the arachidonic acid in a normal subject coincides with the passage of the curve at point zero of ∅C20:4. It is as if, in normal conditions the subject has no flow of arachidonic acid between blood and brain, or rather, the situation is one of equilibrium. The subject, in normal conditions would be in a steady state condition between blood and brain, as regards their exchange of arachidonic acid. In the graph of Fig. 10 what has just been described is reported.
Now, in order to consider a possible shift of the system from the supposed steady state, we give an example, reported in Fig. 11. Let us suppose that, for any reason
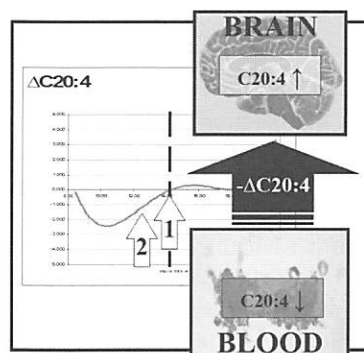

Fig. 11 - *A possible shift of the system from the equilibrium, takes the system itself to such conditions as to tend to return to the starting position, in accordance with the Principle of Le Chatelier*

whatsoever, from the steady state point (in the Figure, light grey arrow 1), the system shifts, for example, into position 2 (in the figure, light grey arrow 2). That would mean a decrease of the arachidonic acid in the vein (from position 1 to 2, the shift in the graph is towards the left) that is transferred to the brain. So there would be a decrease in the vein and an increase in the brain, with the consequent increase in the gradient between the two districts. That gradient would make the system tend to return to the steady state, i.e. to the situation of balance, in agreement with the principle of Le Chatelier[1].

After considering the dynamics around the intersection of the curve with the axis of the abscissa, substantially the central part of the graph, we move on to focus our attention on the far left.
Proceeding from the centre of the graph towards the left, which corresponds to a decrease in the arachidonic acid in the platelet, there is a corresponding increasing in the flow of the acid from the blood to the brain. By continuing to decrease the venous acid content down to very low values (see Fig. 12, part highlighted with the circle), there is an inverse trend of the curve that returns towards zero, that is towards null flow. Indeed, it is reasonable to think that if the platelets continue to release arachidonic acid to the brain, the quantity will be steadily reduced until the flow is completely interrupted (passage from the zero curve to the lower limit).
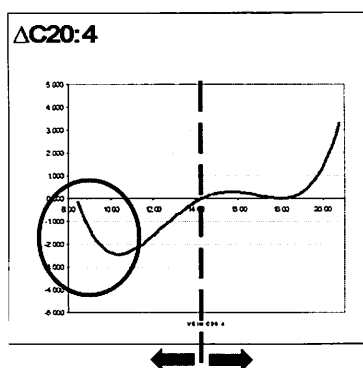Now consider the opposite part of the curve, i.e. very high

Fig. 12 - *Behaviour of the system for very low values of venous arachidonic acid. If the platelets have released all the available acid, the transferable quantity is exhausted and the flow is closed.*

values of arachidonic acid in vein. Suppose then that starting from the intersection of the curve with the axis of the abscissa and proceeding in this case, towards the right. The increase in venous acid is matched by a decrease in the brain and an increase in the flow of the same acid from brain to vein. This is what the graph reported in Fig. 13 shows, (circle). The data relating to the population studied allow us to construct the curve of interpolation up to a quantity of arachidonic acid in the vein equal to about 21% (of total platelets fatty acids). It is legitimate to wonder how the curve would continue with even higher values (Fig. 13). In the obvious absence of experimental data for the human brain, the only thing possible, at this point, is to enter into the realm of hypotheses. Imagine then increasing more and more the quantity of arachidonic acid in the vein, with the consequent reduction in the brain and a flow increase between the two districts (from the brain to the vein): it is legitimate to think that the brain acid reduction will not continue beyond a certain value, it is unthinkable to expect a reduction in the arachidonic acid in the brain down to zero! There would be an inverse trend of the curve eventually cancelling out the flow between the two districts. That is, the curve would continue symmetrically (and opposite) as compared with what happens for very low values of arachidonic acid in the vein, as already illustrated previously. The behaviour hypothesised is depicted in the Fig. 13.
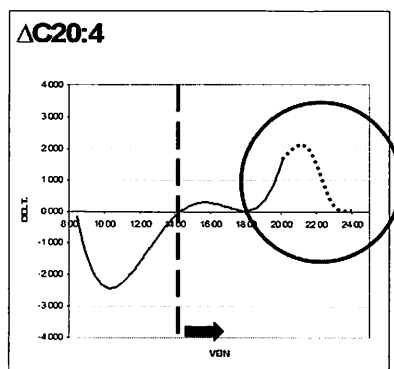

Fig. 13 - *Hypothesis on the dynamics of the arachidonic acid for very high values in the vein. The hypothesised part of the curve is the one outlined.*

If this likely hypothesis were confirmed, what would the situation in the brain and in the platelets be? In the platelet there may be some very high values of arachidonic acid and the flow between brain and platelet may be reduced until it reaches zero: the brain no longer manages to "offload" arachidonic acid in the platelets. It is possible that the brain, no longer able to offload into platelets, could be the site of the accumulation of arachidonic acid. At this point we consider Major Depression. The literature claims that in this disease the platelet level of arachidonic acid is very high (Cocchi M. et al. 2008, 2009), as well as in brain (Green et al., 2005).

If we consider the population of subjects with Major Depression analysed by the authors (Cocchi et al., 2008, 2009), the mean value of arachidonic acid measured would position this population precisely in the zone with a very high level of arachidonic acid in the platelets just described, as illustrated in the Fig. 14.
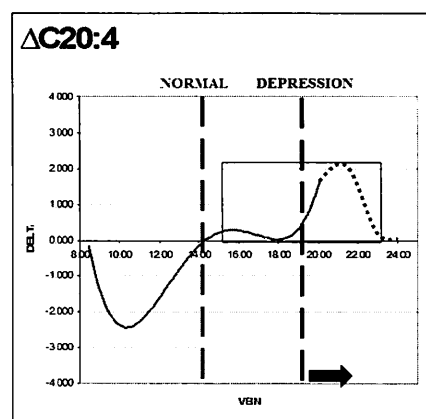

Fig. 14 - *The population of depressed subjects, in the arachidonic acid graph. The mean of the population of the depressed subjects is highlighted with a dark grey line. The black rectangle reports the interval of a standard deviation.*
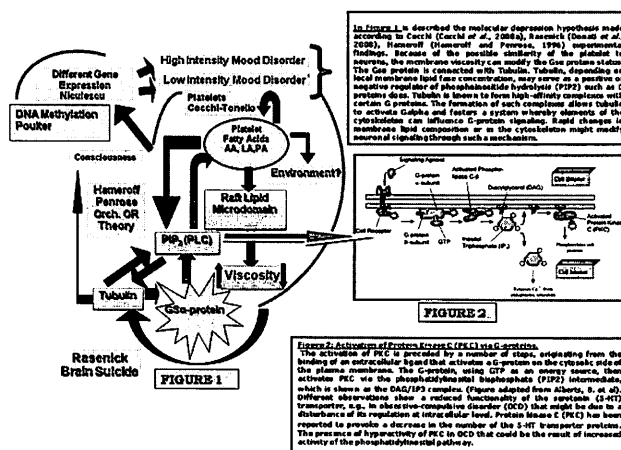

Fig. 15

Conclusion

Substantially, the situation of the subjects affected by Major Depression reported in the literature coincides with the hypotheses and the conjectures put forward. We can thus conclude by summing
up the final conjecture: the high level of arachidonic acid present in the brain of the subjects with Major Depression could be the effect of a sort of saturation of that acid in the platelets. The platelet, in conditions of "saturation", might no longer be able to collect the arachidonic acid in excess with its consequent accumulation in the brain. This is, merely, a suggestive hypothesis to explain a possible biochemical mechanism of the brain and of the depressive disorder.
Among the innumerable secrets that still concern the brain, our hypothesis seems of some interest for the understanding of a possible way to study animal and human routes to depression. According to biomolecular and genetic findings a hypothesis could be made as shown in figure 15. (Donati et al., 2008; Le-Niculescu et al., 2008; Poulter et al., 2008; Rasenick et al. 2004; Quilter et al., 2008; Cocchi et al., 2008, 2009)
Now we present in Fig. 15, the design of the bio molecular depression hypothesis in agreement with biological findings. Because of the possible similarity of the platelet to neurons, the membrane viscosity can modify the Gs protein status. The Gs protein is connected with Tubulin. Tubulin, depending on local membrane lipid fase concentration, may serve as a positive or negative regulator of phosphoinositide hydrolysis (PIP2) such as G proteins does. Tubulin is known to form high-affinity complexes with certain G proteins. The formation of such complexes allows tubulin to activate G and fosters a system whereby elements of the cytoskeleton can influence G-protein signaling. Rapid changes in membrane lipid composition or in the cytoskeleton might modify neuronal signaling through such a mechanism.

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