

## Inhibition of p38-Mitogen-Activated Protein Kinase may Protect from Clozapine-Induced Agranulocytosis

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Despite the clinical advantages of clozapine in the treatment of otherwise therapy-resistant schizophrenia, continuous administration results in neutropenia and life-threatening clozapine-induced agranulocytosis (CA) in about 2.2% and 0.8% of patients, respectively (Atkin et al. 1996). The aetiopathogenesis of these haematogeneous side effects is still uncertain, but there is increasing evidence from *in vitro* (Williams et al. 2000) and *ex vivo* (Loeffler et al. 2003) studies that CA is accompanied by an increased rate of apoptosis of blood neutrophils and probably their late precursors including CD34 positive cells, even under an enhanced endogenous release of the survival factors G-CSF and GM-CSF (Loeffler et al. 2003).

Apoptosis of granulocytes is closely regulated to maintain cellular homeostasis under physiological conditions (Simon 2003). Reactive oxygen intermediates (ROI) play an important role even in spontaneous neutrophil apoptosis (Kasahara et al. 1997). We observed superoxide radical production in neutrophils of clozapine-treated patients (Fehsel et al. 2001) and activation of the p38-mitogen-activated protein kinase (p38-MAPK) is a crucial step in this signal cascade (Figure 1). We found that inhibition of this enzyme by the specific inhibitor SB 203580 in human promyelocytic HL60 leukemia cells, which are closely related to neutrophil progenitors, reduced the percentage of apoptotic cells from 10% to 5% under clozapine treatment (10-50 μM) (Fehsel et al. 2002). Even the spontaneous apoptosis of neutrophils was delayed by SB 203580 or a p38-MAPK-specific antisense oligonucleotide (Aoshiba et al. 1999).

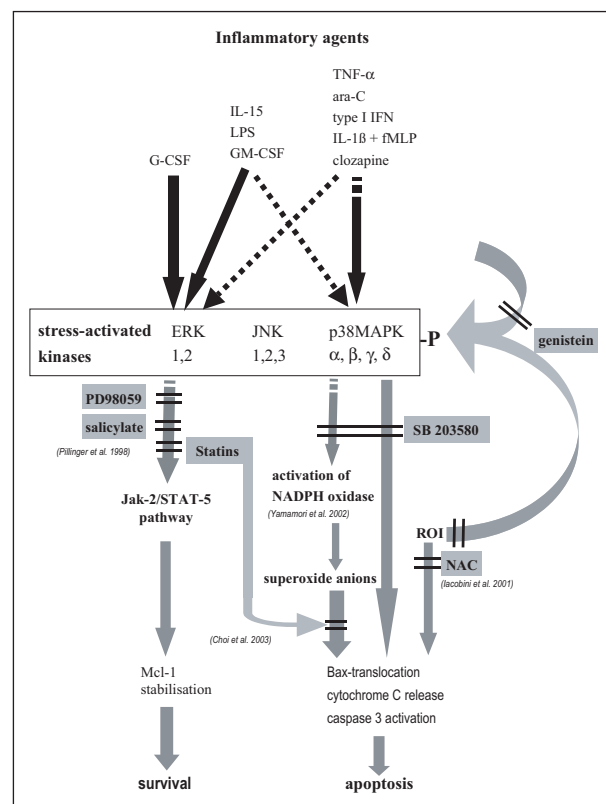
Alternatively, the tyrosine kinase inhibitor genistein blocked apoptosis induced by the highly reactive nitrenium metabolite of clozapine which was applied at therapeutic concentrations (1-3 μM; Williams et al. 2000). One main intracellular target of genistein is indeed p38-MAPK which is activated by tyrosine phosphorylation (Aoshiba et al. 1999). Moreover, p38-MAPK inhibition attenuated the respiratory burst in human neutrophils primed by LPS and stimulated by formyl-methionyl-leucyl-

phenylalanine (Yan et al. 2002) as well as their superoxide release induced by IL-1 beta (Suzuki et al. 2001). In transfected CHO cells which expressed the human 5-HT 1A receptor, clozapine and other atypical antipsychotics activated MAPK whereas the standard neuroleptic haloperidol did not (Cussac et al. 2002). Most importantly, *in vitro* these cytoprotective effects of p38-MAPK inhibition did not interfere with G(M)-CSF mediated signaling (Suzuki et al. 2001), which plays a pivotal role in neutrophil stimulation not only in CA.

We hypothesize that p38-MAPK inhibition in polymorphonuclear leukocytes and their precursors may weaken or prevent CA by specific inhibition of one main proapoptotic signaling pathway (Figure 1). At present, several p38-MAPK-inhibitors are being tested as antiinflammatory drugs in clinical trials (Mclay et al. 2001). If these studies show that the p38 MAPK-inhibitors are well tolerated without affecting the therapeutic effects of clozapine, comedication may help to reduce the risk for CA.

### Figure 1

Stress-activated kinases are differentially involved in apoptosis induction in neutrophils (Simons 2003). While activation of the ERK-pathway results in prolonged survival of neutrophils, activation of the p38 MAPK-pathway leads to oxidative burst and ROI-dependent apoptosis of neutrophils. Depending on the trigger for activation the half-life of neutrophils is heavily effected. Pharmacological intervention is able to shift the balance. In autoimmune diseases and inflammation, glucocorticoids and non-steroid antiinflammatory drugs inhibit ERK-activation, thereby supporting apoptosis of cells. In contrast, during agranulocytosis increased apoptosis is stopped by G-CSF treatment. Prophylactic treatment at the beginning of clozapine medication should therefore avoid general activation of both stress-activated kinases, but either strengthen ERK-activity or inhibit p38-MAPK. Especially, ROI induction should be repressed until endogenous cell proteins protect from oxidative stress-induced apoptosis.



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## Decreasing National Suicide Rates — Fact or Fiction?

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*In his paper, entitled "A Stubborn Behaviour: the Failure of Antidepressants to Reduce Suicide Rates" (World J Biol Psychiatry [2003] 4: 184-191), Professor Herman Van Praag concludes that despite the substantial rise of the prescription of antidepressants "over the past decades the rates of completed suicide has remained quite stable". To demonstrate this statement Professor Van Praag lists in Table 1 of his paper nine countries, in seven of which the national suicide rates really did not decline. There are, however, two major problems with this Table. First, Professor Van Praag shows the suicide rates only between 1980 and 1995 and does not consider the figures already reported for the years 1998-2002. Second, he has completely neglected almost all the countries which showed the greatest decline in their suicide rates between 1980 and 1998/2002. (In addition, there is a misprint in the table, as the suicide rate of Australia in 1995 should be 11.8 and not 1.8.)*

*Table 1 in this Letter displays a quite different picture. It shows the national suicide rates of the 10 countries with the greatest decline in their suicide rates between 1980 and 1998/2002. In the majority of these countries (eight of the 10) the peak was in 1980 or 1985, and nine of them had their lowest rate in 1998/2002. No sophisticated statistical analysis is necessary to accept that the national suicide rates declined dramatically in these countries, and particularly in those which had previously had the highest suicide rates in the world (Hungary, Denmark, Estonia, Austria, Switzerland, Sweden, Finland, etc.). The 54% decrease in Denmark as well as the 30-38% decline in Switzerland, Estonia, Austria, Germany and Hungary is really impressive; a huge increase of antidepressant prescription in the last 10-15 years has been reported from Denmark, Hungary, Sweden and Finland (Isacsson 2000; Rihmer 2001; Rihmer et al. 2001). There is no doubt that a similar increase is present in the other six countries listed in Table 1.*

The suicide rate in Hungary has shown a steady decline from 44.9/100,000 in 1980 to 28.0 in 2002, a fall of 38%, while accompanied by a marked rise in the use of antidepressants (mainly SSRIs after 1990) from 2.4 DDD/1000 people/day in 1984 to 17.5 in 2002, which is about a sevenfold increase. Unemployment and alcohol consumption did not correlate with the decrease in suicide rates (Rihmer 2001; Rihmer et al, 2001; see Figure 1) Very similar findings have been reported from Sweden, Denmark, Finland and Norway between the years 1990 and 1996 (Isacsson 2000). As I have discussed earlier, "since the effect of a given (and effective) intervention largely depends on the baseline situation (i.e., the effect is greater when the baseline situation is more pathological), the role of better recognition and treatment of depression in reducing suicide rates can be easier to demonstrate in the populations when the suicide rate is high and the rate of treated depressions is low. Hungary, Sweden, Finland and Denmark would be the best examples for these." (Rihmer 2001.) Therefore, if we are interested in this subject, we should consider the suicide rates of the countries that have shown the highest suicide mortality in the 1980's.

In addition, a very recent report from Australia (Hall et al. 2003) also shows that changes in suicide rates are significantly associated with exposure to antidepressants in different age cohorts for 1991-2000. In both men and women the higher the exposure to antidepressants, the larger the decline in suicide rate. Considering all the above, it is evident that increasing utilisation of antidepressants is accompanied by a dramatic decline of national suicide rates in several European countries, particularly in those where the suicide rates were previously the highest.

Professor Van Praag quotes me (Rihmer 2001) as follows: "Taking all these data together, I arrive at the conclusion that one can advance only few arguments against the thesis that suicide remained stubbornly present in the era of antidepressants. Rihmer (2001) disagrees. He stated that the antidepressant era has shown a reduction in suicide rate: 'The sometimes presented statement («increasing use of antidepressants did not reduce suicide rates») is counterproductive, rather than a counterargument.' By and large, the available facts, however, do not support this notion. Facts are just facts. They refuse to be qualified as productive or counterproductive. Theses can be qualified as productive or counterproductive. If the thesis represents a desirable condition but the facts are non-supportive, the appropriate thing to do is to analyse the data as to their origin and do one's utmost to generate facts that are supportive."

Professor Van Praag qualifies my statement quoted by him as a "notion", failing to consider that it was based on the facts I had presented above (both here and in my article quoted by him). There can hardly be anyone following the development of present-day psychiatry who would deny the factual existence of

the data of decreasing national suicide rates in several countries. There are, of course, a few colleagues who do not want to see the connection between this fact and the other fact of increasing antidepressant use in the same countries. Of course, the negative correlation between increasing antidepressant prescription and decreasing national suicide rates in several countries does not automatically mean that there is a causal relationship between them. The interpretation of this "connection" might be a subject of further debates. However, considering the strong (and causal) relationship between depression and suicide, also discussed by Professor Van Praag, it is very likely that more widespread treatment of depression is a significant (but not the only) factor in declining suicide rates (Hall et al. 2003; Isacsson 2000; Rihmer 2001).

The sentence "increasing use of antidepressants did not reduce suicide rates" is, I insist, more than false: the opposite is true, and it is true for several countries. This statement is really a dangerous one, because it presents psychiatry as an unproductive medical profession and provides a good argument for decision-makers in health care not to increase the financial support of psychiatry as a whole and of antidepressants in particular.

**Table 1**

National suicide rates of the 10 countries with the greatest decline in the suicide rates between 1980 and 1998/2002

Country	1980	1985	1990	1995	1998/ 2002	Difference (peak minus 1998/2002)
1. Denmark	31.6	27.9	23.9	17.7	14.4	- 54%
2. Hungary	44.9	44.4	39.9	32.9	28.0	- 38%
3. Germany	20.8	16.5	17.8	15.8	13.6	- 35%
4. Austria	25.7	27.7	23.6	22.2	18.3	- 34%
5. Estonia	36.7	22.3	27.1	40.1	27.5	- 31%
6. Switzerland	25.7	25.0	21.9	20.2	18.1	- 30%
7. Sweden	19.4	18.2	17.2	15.3	13.8	- 29%
8. Finland	25.7	24.6	30.3	27.2	22.5	- 26%
9. Czech Rep.	-	20.9	19.3	17.5	16.1	- 23%
10. France	19.4	22.5	20.0	20.6	17.5	- 22%

Source: World Health Organization, Geneva 2003

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